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REVIEW ARTICLE

Adiposity and risk of cardiovascular diseases in Japan: secular trend, individual level associations and causal pathway – implications for the prevention of cardiovascular diseases in societies with rapid economic development

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Abstract In Japan, overweight/obesity in adults defined as a body mass index of 25 kg/m^2 or over has roughly doubled among middle-aged men over the past few decades. In parallel with a population rightward shift in the degree of obesity, the proportion of hypertension attributed to overweight has increased. There is an indication that the incidence of ischemic stroke and coronary heart disease remains stable or has been increasing among men. These facts indicate that the relative importance of cardiovascular diseases (CVD) risk factors may have changed. Although it was confirmed at an individual level that the degree of obesity was positively associated with CVD incidence, there is a sizeable proportion of individuals who are at an increased CVD risk state without being overweight/obese in today's Japan. Thus, further implementation and promotion of activities are needed to bring about meaningful changes in the obesity trend in communities that are harmonized with other domains of CVD prevention activities.

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Introduction

Stroke mortality had been much higher in Japan compared with other industrialized populations until it declined steeply between 1965 and 1990 due mainly to a decrease in the level of blood pressure [1], and by improvement in nutritional status [2]. At the same time, coronary heart disease (CHD) mortality remains as low as one-third to one-fifth of that in the United States [3] even with the westernization of lifestyles that has brought about increases in blood cholesterol levels and the degree of obesity. However, there are some indications that the decline of stroke incidence decelerated or stopped [4, 5], and CHD incidence increased [6, 7]. In this review, we first describe the population trend in the degree of obesity as measured by the body mass index (BMI), and review prospective cohort studies that reported associations of obesity measures and metabolic syndrome (MetS) with cardiovascular diseases (CVD) in Japanese. We then review literature that reported secular and geographical trends in the incidence of CVD subtypes, including ischemic stroke subtypes and percutaneous coronary intervention (PCI) to help our understanding of shifts of CVD risk factors and their determinants, including obesity.

Predictive diagnostics, targeted preventive measures and personalized medicine (PPPM) is a new paradigm proposed by the European Association for Predictive, Preventive and Personalised Medicine [8]. For the primary prevention of CVD, population-based prevention aligned with identification of and intervention to high-risk individuals who have high estimated CVD risk, are essential. In order to enable these activities, cycles of research, formation and implementation of guideline and regulation, and evaluation are necessary. To efficiently and effectively facilitate this process, communication among medical and public health professionals is especially important [9].

From a PPPM perspective, we derive conclusions that implementation and promotion of activities for bringing about meaningful changes in the obesity trend are essential. However, this effort should be harmonized with other domains of CVD prevention activities, such as measures against smoking and salt intake.

Obesity trend in Japan

In Japan, obesity in adults defined as a BMI of 30 kg/m^2 or over [10] has roughly doubled over the past few decades in men, although the absolute prevalence is only 3% [11] in contrast to much higher prevalence in OECD countries (16%, average) [12] or in the United States (34%) [13]. If obesity is defined by a BMI greater than or equal to 25 kg/m^2 (Japanese criterion) [14], 28.6% of men and 20.6% of women were obese in 2008. The average BMIs have been increasing consistently since 1950 except for younger women [11, 15] (Figs. 1, 2). Namely, the average BMI of women aged 30–39 and that of women aged 40–49 have been decreasing from 1975 to 1985, respectively. However, if aging-related changes of BMI by birth cohorts are compared, aging during middle age seems to be related to weight gain on average even in younger generation women (born in 1960's), who weighed less than the older generation at a younger age (30–39), but gained thereafter at least through their sixties (Figs. 3, 4). It is noteworthy that younger generation men enter middle age with a higher BMI, and they experience a continuous increase of BMI. These observations are partly supported by a longitudinal analysis of repeatedly-measured body weight among the same individuals [16].

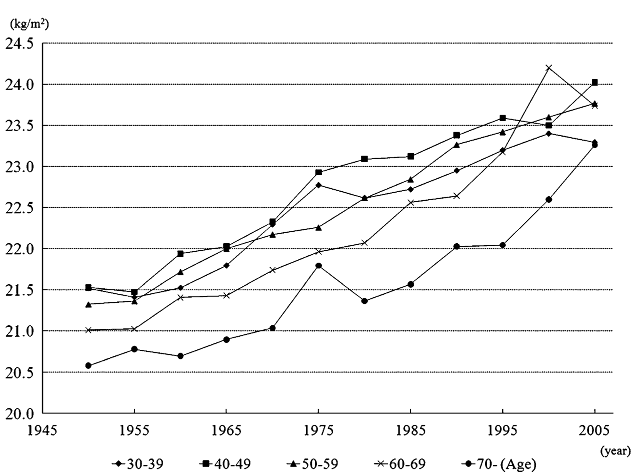

Fig. 1 Secular changes in the mean body mass index in Japanese men, National Health and Nutritional Survey in Japan 1950–2006

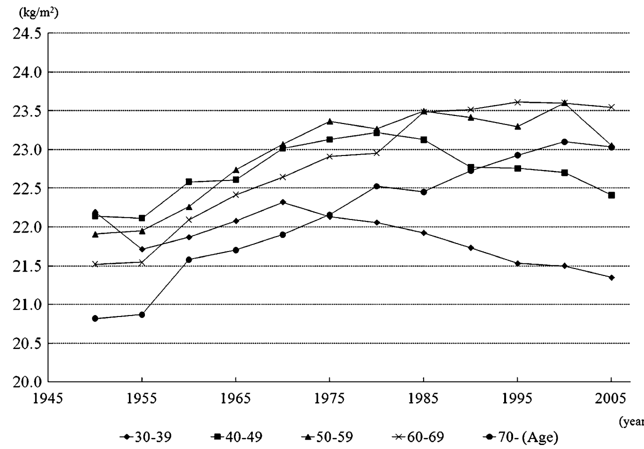

Fig. 2 Secular changes in the mean body mass index in Japanese women, National Health and Nutritional Survey in Japan 1950–2006

Urban and rural difference of obesity trend

It was reported that the mean BMI of men in an urban community has increased from 22.5 kg/m^2 in the earliest survey (1963–1966) to 23.8 kg/m^2 in the last survey (2000–2003) [7] (Table 1). The mean BMI of women in an urban community, however, decreased from 23.4 to 22.8 kg/m^2 during the same period. Contrarily, the mean BMI increased in both men and women in a rural community (22.6 to 24.0 kg/m^2 in men and 23.1 to 24.3 kg/m^2 in women). In the Hisayama Study of a suburban community, the mean BMI also increased from 21.3 kg/m^2 in 1961 to 23.5 kg/m^2 in 2002 in men and from 21.7 to 22.9 kg/m^2 in women [17]. A national survey also found that prevalence of overweight (BMI ≥25 kg/m^2) among men increased regardless of the residential areas, whereas that among women aged 50 or over in urban areas has also been decreasing [18].

Association of degree of obesity with blood pressure

In the same studies that reported secular BMI changes in rural/suburban and urban men and women, mean blood pressure (BP) changes were also described [7, 17]. Although systolic BP decreased in both men and women from either rural/suburban or urban communities, the magnitude of the decrease was more prominent in rural/suburban men and women and in urban women than in urban men. Further, diastolic BP increased in urban men. These observations imply the existence of two sets of factors with opposite directions; one characteristic of previous rural areas and the other more typical of recent urban areas, especially, men. Indeed, hypertension without being overweight used to

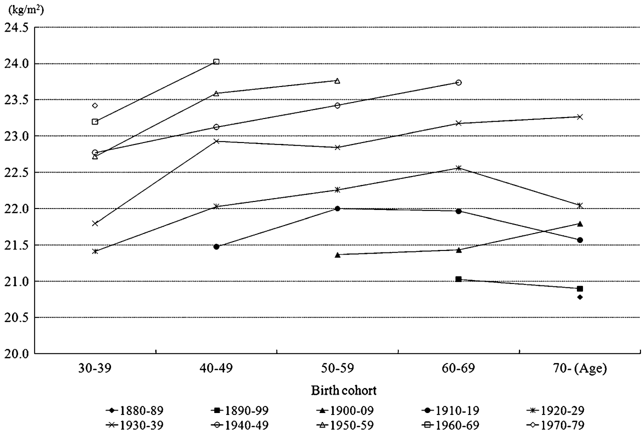

Fig. 3 Changes in the mean body mass index with age by birth cohort of Japanese men, National Health and Nutritional Survey in Japan 1950–2005

constitute a majority of the hypertension cases in rural communities in 1960's, but it decreased significantly by the 1980's [19]. This change was accompanied by increases in overweight and also in the proportion of hypertension among the overweight. Furthermore, a correlation between BMI and diastolic BP was not present in the 1960's in rural men aged 40 to 49; however, it emerged in the 1970's and became stronger in the 1980's. In contrast, the prevalence of hypertension in urban men has been increasing since the 1990's [20]. This is partly due to a continuous increase in the prevalence of overweight, but the authors have suggested other factors besides obesity such as mental stress, increased workload and sleep deprivation since the increase has also been observed in individuals without overweight.

Although further nationwide studies are warranted, hypertension attributed to overweight/obesity is increasing in Japan. Prospective studies have also confirmed the associations [21–23]. Since it was reported that the

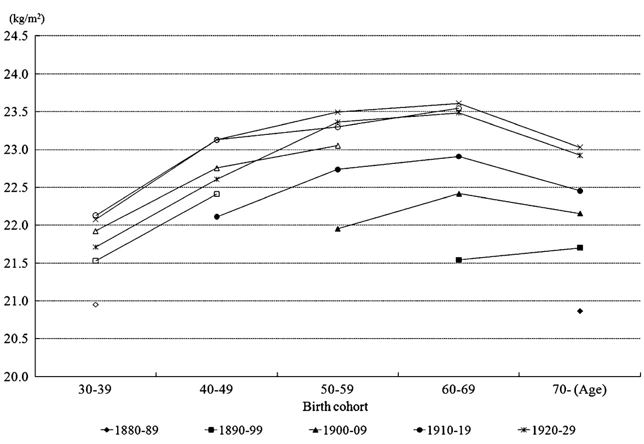

Fig. 4 Changes in the mean body mass index with age by birth cohort of Japanese women, National Health and Nutritional Survey in Japan 1950–2005

strongest risk factor for the development of hypertension was a higher BMI, and that 40% of new hypertension cases was attributed to overweight/obese in US women with 66% of women being overweight/obesity [24], it would be reasonable to take measures against overweight/obesity as one way to prevent hypertension in Japan as well.

Stroke and ischemic stroke subtypes

Ischemic stroke consists of three major subtypes with different etiologies: lacunar, nonlacunar thrombotic (atherothrombotic), and cardioembolic. The underlying vascular or non-vascular pathophysiologies of each subtype differ, such as lipohyalinosis and microatheroma for lacunar stroke, or atherosclerosis for atherothrombotic stroke. Intracerebral hemorrhage (ICH) is also characterized by lipohyalinosis [25]. Lipohyalinosis is arteriosclerosis of the arteriole, and characterized by degeneration of the media of small arteries with replacement of vascular muscle by lipid deposits and collagen (sclerosis) and loss of structural integrity of the vessel wall [26]. Therefore, risk factors for lacunar stroke and ICH overlap, among which hypertension is the most important [27]. The rapid decrease of stroke mortality in Japan since 1965 can be attributed to the decrease in ICH [5], which is due to improvement in hypertension control, the downward shift of population blood pressure distribution and also to improvement in nutritional status manifested as an increase in blood cholesterol level [28]. It was also hypothesized that ischemic stroke subtypes may be shifting from lacunar to atherothrombotic stroke predominance [4, 17], as observed in Western populations [29]. In the Hisayama Study, there was a relative increase of atherothrombotic infarction (22% to 32%) and decrease of lacunar infarction (65% to 41%) in men, although the overall stroke incidence rate decreased from 8.7 in men and 4.3 in women per 1,000 person-years in the first cohort (1961–1973) to 3.9 in men and 2.6 in women in the third cohort (1988–2001) [17]. The proportion of lacunar stroke in an urban community was similar [30] to that in the Hisayama Study (50% to 60% in both men and women), but this study did not find a similar secular trend.

These rapid (about 30-year) trends indicate changes in environment and behavioral factors that would have brought shifts in the risk factors [19]. As stated earlier, overweight/obesity is attributed more to the development of hypertension [19, 20, 31]. Overweight/obesity has other metabolic impacts such as diabetes. Since diabetes is a significant risk factor for all the ischemic stroke subtypes [29], the current overweight/obesity trend may increase the relative importance of diabetes and other metabolic disorders in the development of stroke and its subtypes in the Japanese population [32, 33].

Table 1 Trends in age-adjusted mean body mass index and systolic blood pressure in the Hisayama and the Akita-Osaka Studies

	Men					Women				
	1960’s	1970’s	1980’s	1990’s	2000’s	1960’s	1970’s	1980’s	1990’s	2000’s
Body mass index (kg/m^2)										
Hisayama[a]	21.3	21.7	22.8	NA	23.5	21.7	22.5	22.9	NA	22.9
Akita[b]	22.6	23.1	22.9	23.2	24.0	23.1	24.0	23.9	23.9	24.3
Osaka[b]	22.5	22.3	22.7	23.3	23.8	23.4	22.9	22.6	22.9	22.8
Systolic blood pressure (mmHg)										
Hisayama[a]	162	157	151	NA	148	163	161	154	NA	149
Akita[b]	150	141	136	133	132	142	135	132	129	129
Osaka[b]	135	135	132	131	132	135	130	130	129	128
Diastolic blood pressure (mmHg)										
Hisayama[a]	91	90	87	NA	89	88	87	83	NA	86
Akita[b]	87	86	85	83	86	83	81	80	79	81
Osaka[b]	80	81	80	84	85	80	79	78	80	80

[a] Data for Hisayama was from Kubo et al. [17]

[b] Data for Akita and Osaka were from Kitamura et al. [7]

NA indicates not available.

Mean values of the Hisayama Study were among hypertensive subjects (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or current use of antihypertensive agents)

Measurements were carried out in 1961, 1974, 1988, and 2002 in the Hisayama Study, and in periods 1964–66, 1976–79, 1984–87, 1992–95, and 2000–03 in the Akita-Osaka Study

Associations of obesity measures with ischemic stroke

Findings on the associations of obesity measures with ischemic stroke from individual cohort studies may seem inconsistent (Table 2) with null [34–36], positive association only in women [37–40], and positive association only in men [41]. The reasons for the inconsistency are not clear due to differences in sample sizes, obesity measures and the references used, or covariates in the statistical models; however, baseline years of the studies with null findings are generally old (1960’s to 1970’s). Recently, a pooling project reported a meta-analysis finding based on individual participant data from 16 existing high-quality prospective cohort studies in Japan comprising both rural and urban areas [42]. In this prospective study with 1,113 incident strokes, hazard ratios (HRs) for total stroke, cerebral infarction, and ICH of men with BMI 27.0 kg/m^2 or greater were 1.80 (95% confidence interval: 1.31–2.47), 1.86 (1.28–2.69), and 2.19 (1.10–4.38) compared to those with BMI less than 21.0 kg/m^2. The respective values in women were 1.64 (1.24–2.16), 1.68 (1.16–2.43), and 1.75 (1.01–3.05). These associations, especially of ICH, were found to be mediated by systolic BP. Thus, it is plausible that BMI is positively associated with cerebral hemorrhage and infarction, and that overweight/obesity increases stroke risk partly through the elevation of BP. Yet, it is still unknown why earlier studies did not find a significant association between BMI and stroke incidence. Recently, the population attributable fraction (PAF) of normal and higher BP in reference to optimal BP (systolic BP <120 mmHg and diastolic BP <80 mmHg) for stroke incidence [43] were reported to have decreased from the earliest cohort initiated in the 1960’s to the latest cohort started in the 1980’s, and which were considered to suggest an increase in the contribution of other, possibly obesity-related, factors [44]. Indeed, PAF of obesity to cerebral infarction increased gradually from 6% in the first cohort to 9% in the third cohort in the Hisayama Study, although the statistical significance of the difference was not indicated in this study [17]. Since obesity is associated with a wide range of CVD risk factors, positive associations between obesity measures and each ischemic stroke subtype were also reported from the Atherosclerosis Risk in the Communities Study consisting of African-Americans and Caucasians in four US communities [45]. Collectively, avoidance of obesity offers the potential of reducing stroke in Japan.

Increasing trend of CHD in middle-aged urban men

In the Akita-Osaka Study, clinical data on PCI have also been collected since 1980, and a significant increase in the incidence of CHD was observed between the periods 1980 to 1987 and 1996 to 2004 among urban (Osaka) middle-aged

Table 2 Cohort studies reporting associations of obesity measures with cardiovascular diseases in Japanese

Study	Study period	Population	Endpoint	Findings
Hisayama Study (Yonemoto et al., 2010) [41]	1988–2000	2,421 residents in a suburban community aged 40–79	Stroke (107 cerebral infarction and 51 ICH)	BMI ≥23.0 kg/m^2 was associated with increased CI incidence only in men compared with BMI <21.0 kg/m^2. The association was independent of mediators including systolic blood pressure, ECG abnormalities, and diabetes.
Hisayama Study (Tanizaki et al., 2000) [40]	1961–1993	1,621 residents in a suburban community aged 40 or over	Cerebral infarction subtypes (298 cerebral infarction cases, 56% lacunar)	Continuous BMI was positively associated with lacunar stroke incidence only in women independent of age, systolic blood pressure and ECG-LVH.
JPHC Study (Chei et al., 2008) [23]	1990–2001	43,235 men and 47,444 women aged 40–69 living in nine administrative areas each covered by a public health center	CHD (399 in men and 119 in women)	Compared with BMI 23.0–24.9 kg/m^2, BMI ≥30.0 kg/m^2 was associated with higher incidence of CHD only in men in age- and multivariate-adjusted models.
JPCH Study (Saito et al., 2010) [37]	1990–2005	32,847 men and 38,875 women aged 40–69 living in nine areas	Total stroke (1,181 in men and 838 in women) Stroke subtypes (1,143 cerebral infarction, 616 ICH and 251 subarachnoid hemorrhage)	BMI was positively associated with cerebral infarction and ICH incidence only in women. The associations were independent of histories of hypertension and diabetes.
Suita Study (Furukawa et al., 2010) [38]	1989–2005	5,474 residents in urban communities aged 30 to 79	CVD (207 strokes and 133 myocardial infarctions)	Waist circumference 84 cm or greater (top quartile) was associated with increased stroke incidence only in women compared with the lowest quartile (waist circumference <70 cm).
JALS (Yatsuya et al., 2010) [42]	Baseline year ranged from 1985 to 1999	Meta-analysis of 16 cohorts using individual data (n= 45,235, ages 40 to 89). 82.7 % of the participants were from communities and 17.3 from work-site.	CVD Total strokes (n=1,113) Cerebral infarction (n=725) ICH (n=229) Myocardial infarctions (n= 190)	Incidence of cerebral infarction and ICH were positively associated with BMI in both men and women. Most BMI association with stroke incidence was explained by systolic blood pressure. BMI was positively associated with myocardial infarction only in men. The association was not totally explained by total cholesterol and systolic blood pressure.
CIRCS (Iso et al., 2007) [39]	1975–2001 (baseline year varies by communities)	9,087 residents in five communities aged 40 to 69.	Ischemic heart disease (n= 116) Cerebral infarction (n=256)	Overweight (BMI ≥25.0 kg/m^2) was associated with ischemic heart disease in men and cerebral infarction in women. The associations were not independent of confounding variables and serum total cholesterol.
Shibata Study (Nakayama et al., 1997) [35]	1977–1992	2,302 residents in a rural community aged 40 or over	Total stroke (n=142) Cerebral infarction (n=76) ICH (n=27)	There were no significant associations between relative weight and cerebral infarction and ICH incidence (insignificant positive association).
Taisho Study (Tanaka et al., 1982) [34]	1967–1977	772 men and 901 women who lived in a rural community aged 40 or over	Total stroke (n=115) Cerebral infarction (n=81) ICH (n=30)	There were no significant associations between relative weight and cerebral infarction and ICH incidence (insignificant inverse association).

Table 2 (continued)

Study	Study period	Population	Endpoint	Findings
Honolulu Heart Program (Curb and Marcus, 1991) [36]	1965–1985	7,585 men of Japanese ancestry living in Hawaii aged 45–65	CHD and stroke	BMI was associated with CHD incidence in both hypertensive and nonhhpertensive men. BMI was not associated with stroke incidence in either hypertensive or nonhypertensive men.
Ni-Hon-San Study (Robertson et al., 1977) [49]	1968–1970 (Hawaii) 1965–1972 (Japan)	1,963 residents in Japan and 7,705 in Hawaii aged 45–68	CHD (n=47 in Hawaii and 22 in Japan)	Relative weight was associated with CHD in men in Hawaii but not in men in Japan.

men [7]. Age-adjusted incidence of myocardial infarction increased from 45 per 100,000 person-years in the 1960's to 90 in the last survey period between 1996 and 2003. CHD including PCI increased from 56 per 100,000 person-years in the 1980's to 127 in the aforementioned last survey period. A previous autopsy study revealed that the pathology of myocardial infarction among urban men included a larger infarction associated with hypercholesterolemia-derived atherosclerosis of the coronary arteries as observed in Western populations compared to that found in rural men, which was smaller and disseminated infarction associated with hypertension-derived atherosclerosis of coronary arteries [46]. Therefore, the increase of CHD among middle-aged urban men from the 1980s could be due to a concurrent increase in mean total cholesterol level and BMI. AMI incidence rates in rural/suburban men were also reported to have increased in the Takashima AMI registry from 66.5 per 100,000 person-years in 1990–92 to 100.7 in 1999 to 2001 [47]. In the Hisayama Study, however, CHD incidence was shown to be constant from the first to the third cohort for both men and women [48], except in men aged 80 or over who experienced a linear increase (statistical significance of the trend was not indicated in this study).

Associations of obesity measures with CHD

Due to the small number of incidents in women, most previous studies in Japan did not find an association of the degree of obesity with the CHD incidence in women (Table 2). In the Ni-Hon-San Study, relative weight was not associated with CHD; however, the number of CHD cases was very small (n=22 in Japan) [49]. Later studies generally found positive associations between BMI and CHD in men. BMI was positively associated with CHD in the Honolulu Heart Program [36]. BMI ≥25 kg/m^2 was associated with an increased incidence of ischemic heart disease in men in the CIRCS Study [39]. BMI ≥30 kg/m^2 was associated with an increased incidence of CHD compared to those with BMI 23.0–24.9 kg/m^2 in the JPHC Study [23]. In the aforementioned pooling project of existing cohort studies, the association in men was confirmed: compared to those with a BMI of less than 21.0 kg/m^2, HR for MI of men with a BMI of 27.0 or greater was 2.84 (1.52–5.29) and that of women was 1.13 (0.47–2.74) [42]. Further, adjustment for total cholesterol, systolic BP, high-density lipoprotein cholesterol, and diabetes, possible mediators, did not totally explain the association between BMI and myocardial infarction. The authors suggested the existence of other unmeasured factors that mediate the association, such as prothrombotic factors or low-grade systematic inflammation, and implied that avoidance of obesity offers the potential of reducing CHD in Japan.

Table 3 Components of metabolic syndrome in Japan [51]

Abdominal obesity (obligatory component)	≥85 cm in men and ≥90 cm in women
Raised blood pressure	Systolic blood pressure ≥130 mmHg or
	Diastolic blood pressure ≥85 mmHg
Dyslipidemia	Triglycerides ≥150 mg/dl or
	High-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women
Raised fasting glucose	Fasting glucose ≥100 mg/dl

Risks related to metabolic syndrome and its screening

Metabolic syndrome (MetS) is a cluster of risk factors for CVD and type 2 diabetes mellitus, which occur together more often than by chance alone [50].

Although various diagnostic criteria have been proposed by different organizations [50], the risk factors included are generally common: raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and abdominal obesity. While the criteria proposed by the International Diabetes Federation (IDF) as well as the fact that Japanese made abdominal obesity an obligatory component [51] (Table 3), the criteria of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) do not mandate abdominal obesity as a required risk factor; three abnormal findings out of five will qualify a person for the MetS.

The goal of population-based screening of MetS would be to identify a risk state for the development of CVD and diabetes in order to intervene. To maximize public health, the tool used must not overlook a substantial proportion of high-risk individuals, who eventually develop the conditions. In a European population-based study, non-obese people with two or more IDF MetS factors were less prevalent than IDF MetS individuals, but their CVD mortality rate was comparable to that of individuals with IDF MetS [52]. The PAF calculated from the data was 10.0% for men with two or more risk factors without abdominal obesity and 28.2% for men that met IDF MetS criteria. This suggests that IDF criteria would miss at least an opportunity to provide interventions to such individuals. In Japan, there were reportedly more non-overweight individuals with a constellation of risk factors than overweight individuals with the same constellation (i.e., IDF MetS equivalent) in the general population, with both groups having a similar mortality risk [53]. Hence, the PAF was reported to be greater in non-overweight individuals with two or more risk factors (9.4%) than in overweight individuals with the same number of risk factors (7.8%). As similar findings were repeatedly reported [54–58], there has been concern regarding the appropriateness of the public health screening that currently excludes such individuals from the diagnosis of MetS in Japan. Therefore, at the screening level, focusing only on the abdominal obesity-prerequisite IDF MetS cannot be recommended in current Japan where a large proportion of individuals are in a risk state for CVD without being overweight. Nevertheless, IDF MetS is easy to understand pathophysiologically, and interventions targeting abdominal obesity have proved to be effective [59]. The reason is yet unclear for the high prevalence of a risk factor constellation without being overweight in Japan. How to effectively intervene in such cases must also be investigated.

Concluding remarks and outlook

Obesity is a major health concern for most of the world given its already high prevalence. Obesity prevalence has doubled or tripled in many countries since 1980, and is still projected to increase. Even though various measures and actions have been undertaken to avoid fulfillment of this projection, it is almost certain that an obesity epidemic persists. This epidemic seems to have been affecting some age-, sex-, and area-subgroups of the population disproportionately. However, overall and recent trends do not seem to differ considerably.

Even in a relatively lean population like the Japanese, an association has been established between adiposity and CVD risk factors, including hypertension, diabetes mellitus, and dyslipidemia. Thus, the notion that obesity confers increased CVD risk seems plausible. However, there is a sizeable proportion of individuals who are at an increased CVD risk state without being currently overweight/obese. Public health activities to prevent CVD and promote population health should not overlook this fact.

Although a current public health screening and intervention program in Japan that started in 2008 has considerably raised public awareness of obesity and metabolic syndrome, it overemphasized measures to deal with abdominal obesity to the detriment of predictive diagnosis and targeted prevention. Consequently, the intervention program has tended to overlook the opportunity to intervene with non-obese high risk individuals, such as lean hypertensives. More extensive communication is necessary among medical and public health professionals as well as health and insurance administrators to amend the act for this program [60]. We conclude that further implementation and promotion of activities to bring about meaningful changes in the obesity trend in rural and urban communities are needed. However, such activities should be harmonized with other domains of CVD prevention activities.

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