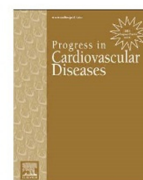


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Worksite Wellness for the Primary and Secondary Prevention of Cardiovascular Disease in Japan: The Current Delivery System and Future Directions

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ABSTRACT

In the Japanese workplace, employers are required to provide annual health checkups for workers in accordance with the "Industrial Safety and Health Law," which also mandates that an occupational physician be assigned to companies employing at least 50 workers. The annual medical examination includes testing for the early detection of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and the metabolic syndrome. This approach has successfully contributed to the extremely low incidence of coronary artery disease among Japanese workers. However, problems such as poor health and the low rate of participation in health checkups among small-scale companies still persist. Furthermore, although most wellness delivery systems in Japan employ strategies targeting high-risk individuals, instituting a strategy addressing the broader population irrespective of screening may be effective in reducing disease risk in the overall population. As a future direction, we should therefore develop practical methods for implementing a population strategy.

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Current system for cardiovascular disease prevention in the Japanese worksite

Today, the majority of the Japanese population undergo annual health checkups. More specifically, approximately 70% of men and 60% of women over the age of 20 receive some type of health examination at least once a year.¹ Mass health screening is offered to all individuals in Japan at the worksite, school, community, and so on. In the workplace, employers are required to provide annual medical examinations for workers, and workers are likewise mutually obligat-

ed to participate in health evaluations. These requirements are prescribed by Article 66 of the "Industrial Safety and Health Law,"² which was established in 1972.

The primary aim of the annual health examination is to identify general health problems among the workers. Article 44 of the "Ordinance on Industrial Safety and Health"³ lists the health conditions to be assessed in the medical evaluation; these vary according to the changing epidemiology of diseases. For example, mortality due to tuberculosis is decreasing since the end of the Second World War, whereas the prevalence of non-communicable diseases (NCDs) such as

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Abbreviations and Acronyms

3M Study = Morbidity of Myocardial Infarction Multicenter Study in Japan

BP = blood pressure

CAD = coronary artery disease

CVD = cardiovascular disease

DM = diabetes mellitus

HDL = high-density lipoprotein

HIPOP-OHP = High-risk and Population strategies for occupational Health Promotion Study

HR = hazard ratio

HTN = hypertension

JMS = Jichi Medical School

LDL = low-density lipoprotein

MetS = metabolic syndrome

MI = myocardial infarction

NCDs = non-communicable diseases

PA = physical activity

WHO-MONICA = World Health Organization-multinational monitoring of trends and determinants in cardiovascular disease

hypertension (HTN) and diabetes mellitus (DM) is increasing. Since 1990, the annual medical examination has included items for the early detection of NCDs.

Additionally, since 2001, all workers are eligible to receive a “worker’s-accident secondary medical examination” following the routine health check-up through the workers’ accident compensation insurance system. The purpose of this examination is to facilitate early detection of NCDs and related complications, particularly, cardiovascular disease (CVD). Several factors led to the addition of this secondary medical examination. First, it was recognized that the number of CVD cases triggered by excessive workload was increasing. Second, the majority of these cases tended to harbour underlying sub-clinical atherosclerosis

occupational physician who meets at least one of the requirements specified in Article 14 of the “Ordinance on Industrial Safety and Health.”³ There are approximately 83,000 occupational physicians in Japan.⁴ One of the most important jobs of the occupational physician is primary prevention of NCDs in the worksite. On the basis of the medical examination, the occupational physician can order workers with abnormal findings to be re-examined or refer them for consultation with other medical specialists. Workers seeking consultation from specialists can readily access any medical institution through the ‘Kaihoken’ system, health insurance for all, which was established in Japan in 1961. ‘Kaihoken’ ensures free access to all types of health services with a self-pay rate of 30% applied across all citizens in Japan. This system is also credited with playing an important role in reducing stroke mortality in Japan after the mid-1960s.⁵

Prevalence of CVD risk factors and incidence of coronary artery disease in Japanese workers

With regard to CVD subtypes, the incidence of coronary artery disease (CAD) is much lower in Japan than that observed in Western countries⁶; however, a high-fat diet,⁷ and reduced physical activity (PA) are anticipated to increase the incidence of CAD. In fact, both the total cholesterol concentration and body weight of the Japanese population have continued to rise over the past 20 years with the prevalence of DM also increasing.⁸

Although many previous cohort studies have investigated risk factors for CVD in the Japanese general population,^{9,10} well-designed studies on CVD risk factors in Japanese workers are scarce. Among the few studies, the Morbidity of Myocardial Infarction Multicenter Study in Japan (3M Study)^{11–13} investigated the morbidity from acute myocardial infarction (MI) and risk factors for MI in Japanese workers. Employing definitions for MI and CAD death established by the World Health Organization-Multinational MONitoring of trends and determinants in Cardiovascular disease (WHO-MONICA) Project, the 3M Study identified a total of 297 fatal and nonfatal CVD events among 133,099 workers (109,550 men, 23,549 women) from 41 workplaces during the period from April 1994 to March 1997, and 257,440 workers (207,310 men, 50,130 women) from 76 workplaces from April 1997 to March 2000. Full-time occupational physicians provided care, and most workplaces participating in the 3M Study represented major companies in Japan. Up to 97.8% of workers aged 40 or older in the study worksites participated in annual health checkups. The age-standardized annual event rate of MI for men aged 35–64 years was 40.2 per 100,000 persons.¹¹ Among the male workers, the crude annual event rates per 100,000 persons were 0 for those in their 20’s, 2.5 for ages 30–34, 7.6 for ages 35–39, 17.7 for ages 40–44, 52.4 for ages 45–49, 67.7 for ages 50–54, and 71.9 for ages 55–59. These figures were significantly lower compared with those previously reported in Japanese coeval community dwellers.

The reduced frequency of MI events among the workers in this study may be attributable to preventive interventions as

sis and/or related risk factors, but neglected to seek intervention; thus, these high-risk workers may be very fragile when overworked. Third, because most atherosclerotic diseases are caused by inappropriate lifestyle habits, it is important to identify early risk factors for each individual in order to provide appropriate guidance and implement suitable measures that can improve lifestyle. Intervening at an early stage may also prevent symptomatic atherosclerotic diseases and reduce ‘Karoushi,’ death due to overwork.

The “worker’s-accident secondary medical examination” consists of the following: a) fasting blood tests, including serum high density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, blood glucose, and haemoglobin A1c; b) exercise electrocardiography or echocardiography; c) carotid ultrasonography; and d) tests for microalbuminuria. Based upon the results of the secondary examination, workers who are deemed to be high-risk due to angina on exertion, the presence of CVD, DM, or other conditions, are immediately referred to an appropriate hospital for further management. Workers who are not high-risk receive “A Special health guidance” from a doctor or public health nurse in order to improve their lifestyle.

The “Industrial Safety and Health Law”² mandates that companies employing at least 50 workers must assign an

well as the early treatment of CAD risk factors. In the 3M Study, 12% of men and 5.6% of women had HTN [blood pressure (BP) $\geq 140/90$ mmHg], 26.5% and 25.8%, respectively, had hypercholesterolemia (total cholesterol ≥ 220 mg/dl); and 11.4% and 4.0%, respectively, had abnormal glucose tolerance (fasting blood glucose ≥ 110 mg/dl). Body mass index ≥ 26.4 (equivalent to the obesity index $+20\%$) was reported for 11.5% of men and 11.7% of women; 55% of men in their 40's and 48.7% of those in their 50's were smokers compared with 24.0% and 16.3% for women in these age categories, respectively.

The 3M Study was designed as a nested case-control study.¹² For each case of MI entered into the study between 1997 and 2000, two age-matched controls were randomly selected from participants in risk factor surveys who had no history of MI. A total of 723 male employees (241 cases and 482 controls) aged 35–65 years were enrolled. Compared to controls, the subjects had significantly higher serum LDL-cholesterol and triglyceride levels, and lower HDL-cholesterol levels. Using conditional logistic regression, predictive models were also constructed to evaluate the risk of MI on the basis of CAD risk factors.¹³ The multivariable conditional odds ratios (95% confidence intervals) for MI were 2.02 (1.29–3.16) for high BP, 2.33 (1.51–3.59) for high LDL-cholesterol, 4.16 (2.36–7.33) for low HDL-cholesterol, 1.49 (0.94–2.35) for high triglycerides, 1.46 (0.89–2.39) for high glucose, and 2.95 (1.90–4.59) for current smoking. The predictive value for MI was markedly reduced after excluding high LDL-cholesterol (change in predictive value, -3.4%), and further exclusions of low HDL-cholesterol (-7.1%) and current smoking (-16.4%). Both high LDL-cholesterol and low HDL-cholesterol levels were independently associated with an increased risk of MI. Additionally, current smoking was highly predictive of MI among middle-aged men, which was a specific feature of Japanese male workers.

A new trial for further wellness: population strategy

Lifestyle modifications such as changes in diet and increased physical activity are important for controlling the risk of developing CVD. Interventional approaches to improving lifestyle may consist of both high-risk and population strategies.^{14,15} The high-risk strategy identifies and reaches out to individuals who are more vulnerable for developing diseases. Most medical services including health checkups as previously described are categorized as high-risk strategies. While the high-risk strategy can be readily understood and strongly motivates individuals to modify their behaviour, it may not affect the majority who fail to meet the criteria for screening high-risk individuals. Therefore, a high-risk strategy may not significantly decrease the overall CVD risk in the population. To effectively reduce the prevalence of a specific disease in the broader population, it is necessary to lower the average risk associated with each risk factor in the population, even if the reduction is minimal. A population strategy, which is more moderate, but universally applied to all

without screening, may be effective in reducing the risk of disease in the entire population.

When implementing a population strategy, it is important to first evaluate the working environment and the employees' lifestyles, and then, implement appropriate interventions. Table 1 presents sample components of a population strategy to control risk factors for CVD. Lifestyle improvements such as dietary modifications (e.g., reducing salt intake or alcohol consumption), increasing PA, and smoking cessation can reduce or prevent CVD risk factors such as HTN, dyslipidemia, and DM. Therefore, it is essential to include initiatives that target the three factors, namely, nutrition, physical activity, and smoking when implementing the population strategy to control CVD risk factors.

In 1998, we initiated a large intervention trial, the High-risk and Population strategies for occupational Health Promotion Study (HIPOP-OHP Study). The HIPOP-OHP Study incorporated a program aimed at reducing the development of CVD risk factors in the workplace. Details of this study have been published elsewhere.^{16–20} Briefly, we recruited 12 companies in Japan, each of which had 500–1,000 employees. The employees at these companies, including two non-factory companies and 10 factories, were assigned to either an intervention or control group. In the intervention group, the health-related environment was improved using a population strategy and individual interventions (high-risk strategy). Interventions in the population strategy (Table 1) were pragmatically introduced. In the control group, only individual intervention teaching material was provided. The baseline survey was conducted between 1999 and 2000, and the intervention program was implemented between 2000 and 2004. In the intervention group, information on diseases and lifestyle modification for all was provided. Posters and stand-type Point of Purchase advertising menus were placed on tables in the dining rooms at the workplaces.²¹ In addition, health-related events were organized through internal websites. To improve nutrition, the contents of meals served in the workplace dining rooms and box lunches delivered by caterers were evaluated, followed by recommendations for sodium and potassium intake, nutritional balance, and fat caloric intake. For PA, walking paths were constructed or walking maps were prepared. An "Active Point Campaign" using pedometers was arranged twice a year to promote individual and interdepartmental competition and increase PA among workers. To reduce smoking, designated smoking areas were established based on the advice of the specialist team. In addition, smoking cessation campaigns were conducted. These interventions were performed in 6-month cycles.

In this study, the absolute (percent) changes in HDL-cholesterol were 2.7 mg/dl (4.8%) and -0.6 mg/dl (-1.0%) in the intervention and control groups, respectively.²² Differences between the two groups with regard to changes in serum HDL-cholesterol levels were highly significant. Heightened awareness of the benefits of exercise achieved through environmental rearrangement and health promotion campaigns, particularly those targeting walking, may have contributed to favourable changes in serum HDL-cholesterol levels. The smoking cessation rate, defined as abstinence

Table 1 – Components of a worksite population strategy for controlling the cardiovascular disease.

Nutrition	Physical activity	Smoking
1. Presenting information for a healthy diet a. Place stand-type mini-poster presentation on the table weekly: 'Point of Purchase advertising menu (POP menu)' b. Wall posters c. Website d. Intra-workplace newspaper 2. Interventions for the workplace dining room a. Assess salt concentration in miso soup b. Change soy sauce servings c. Use low-calorie salad dressing d. Serve healthy menus e. Disclose nutritional balance of menus 3. Inspect total sales of beverages a. Grocery store in the workplace b. Vending machine in the workplace 4. Interventions for the household a. Provide health education for the person who cooks b. Present healthy menus for the household	1. Presenting information for physical activity c. Place stand-type mini-poster presentation on the table weekly: 'Point of Purchase advertising menu (POP menu)' a. Wall posters b. Website c. Intra-workplace newspaper 2. Campaign for increasing physical activity a. Self-recorded diary for physical activity 'active point campaign' b. Lecture on 'active walking' c. Lecture on 'stretching' d. Sport events in the workplaces 3. Installation of areas or tools for walking a. Construct walking paths in the workplaces b. Create maps for walking in or near the workplaces c. Distribute pedometers to all workers	1. Presenting information for smoking cessation d. Place stand-type mini-poster presentation on the table weekly: 'Point of Purchase advertising menu (POP menu)' a. Wall posters b. Website c. Intra-workplace newspaper 2. Antismoking campaign a. Recruit for smoking cessation program, smoking cessation program done by clerical staff 'without nicotine replacement' 'with nicotine gum' smoking cessation program done by medical staff 'with nicotine patch' b. Lecture on 'stop smoking' c. Lecture on 'promotion of smoking area designation' for managerial workers 3. Advise reconstruction to promote designated smoking area 4. Inspect designation of smoking areas

from smoking for the preceding six months or longer, was assessed at 36 months after the baseline survey using a self-administered questionnaire; this rate was significantly higher in the intervention than control group (12.1%, vs. 9.4%, respectively).²³ The study also suggested that designating a smoking area may be effective for preventing DM.²⁴ This measure can be implemented at workplaces where the prevalence of smoking is high. In the real-world setting, however, recent budgetary constraints may prohibit generalization of these health-promoting activities across all occupational settings in Japan.

Residual problems and future direction for solutions

As previously discussed, several health laws and programs have been demonstrated to be effective in preventing CVD among workers in Japan. In April 2008, the Ministry of Health, Labour and Welfare implemented a new strategy for preventing CVD not only in community dwellers but also in worksites in Japan.²⁵ Under this new system, measures for preventing CVD and diabetes such as screening for the

metabolic syndrome (MetS) and subsequent lifestyle modification are available to all citizens (Table 2). Measurement of waist circumference was introduced as an additional item in health checkups. Cardiovascular risk factors are often clustered with abdominal fat accumulation, which has resulted in a high incidence of CVD.^{25,27} Previous cohort studies in Japan have suggested that CVD risk factor clustering was strongly associated with CVD,^{27–29} which has also been correlated with increased medical expenditures.³⁰ We believe it is feasible to focus on MetS in the worksite, as demonstrated in a recent urban cohort study which showed that applying a standard MetS definition is useful for detecting high-risk individuals, particularly in the middle-aged population, but not in the elderly.³¹ MetS screening rates over the past five years, however, has been very low (i.e. less than 35%), especially among small scale companies, self-employed individuals, farmers, fishermen, and other similar workers.

The health status of workers in small companies is relatively poor compared to that of workers in large companies. In 1986, Miyake³² found that the proportion of persons who checked their BP annually decreased commensurately with the size of companies participating in the survey. In 1992, Hirai et al.³³ examined the relationship between HTN and company size and found that in a total population of

Table 2 – Current check-items for annual health check in worksite.*

1. Investigation of anamnesis and work history
2. Examination for the presence of subjective and objective symptoms
3. Examination of height, weight, abdominal circumference, eyesight, and hearing
4. Thoracic X-ray examination and sputum examination
5. Blood pressure measurement
6. Anemia examination (hemoglobin, erythrocyte count)
7. Hepatic function (AST, ALT, γ -GTP)
8. Blood lipid levels (LDL cholesterol, HDL cholesterol, triglyceride)
9. Blood sugar level
10. Examination for the presence or absence of sugar and protein in the urine
11. Electrocardiography

Abbreviations: ALT, alanine transaminase; AST, aspartate amino-transferase; γ -GTP, gamma glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

* Prescribed by Article 44 of the “Ordinance on Industrial Safety and Health” since 2008 when nationwide screening for metabolic syndrome was introduced.

89,299 men, the prevalence of HTN was significantly higher in those working in small-scale companies compared to that in workers from large-scale companies, irrespective of business type. Similarly, the prevalence of HTN was significantly higher in women employed in small-scale companies for some categories of business. Yamataki et al³⁴ also surveyed 6,480 workers of a Japanese steel company and various subcontractors who received health checkups in 2003 and noted a significant trend for a higher prevalence of DM and HTN in smaller companies. A large study³⁵ of 9,833 companies employing a total of 436,729 workers showed that the age-adjusted percentages of male workers in small scale companies (i.e. ≤ 49 employees) with HTN, impaired glucose tolerance, and obesity were 8.5, 5.0 and 3.5%, respectively, which were higher than the respective percentages in companies with ≥ 50 employees. These findings may be explained by the “Industrial Safety and Health Law,” which requires an occupational physician to be assigned to companies with at least 50 workers.

Above-mentioned studies have also suggested that socioeconomic status, including educational level, and control of CVD risk factors may be poor in workers in small-scale companies. A demographic finding in modern society is the inverse association between socioeconomic status and mortality.^{36,37} The Jichi Medical School (JMS) cohort investigated mortality risks in relation to occupational category and position among Japanese workers.³⁸ A total of 6,929 Japanese workers aged 40 to 65 years (3,333 men and 3,596 women) from 12 rural communities across Japan were followed over 10 years. Among the men employed in blue-collar jobs, all-cause mortality was increased compared with that in white-collar workers [hazard ratio (HR): 1.64, 95% CI 1.10–2.45]. Men in blue-collar jobs also showed a tendency for a higher risk of mortality associated with CVD compared with those in white-collar jobs, but the difference was not significant (HR: 1.84, 95% CI 0.69–4.89). On the other hand, when stratified by

occupational category, non-managerial women in blue-collar jobs exhibited a reduced risk for CVD mortality risk compared with managerial women (HR: 0.15, 95% CI 0.03–0.81). However, non-managerial women in white-collar jobs had a non-significant increase in the risk for CVD mortality compared with managerial women (HR: 2.34, 95% CI 0.25–21.87). Based on these findings, the authors concluded that socioeconomic disparity, as defined by occupational category, was related to the risk of all-cause mortality among Japanese men. Further, a potential interaction may exist between occupational category and position with regard to CVD mortality among Japanese women.

The Industrial Safety and Health Law, which is applicable to all companies irrespective of size, mandates employers to offer health examinations to employees. Whereas employers failing to comply are subject to criminal punishment, there is no criminal punishment for non-compliant employees. Furthermore, it is difficult for the Labour Standards Inspection Office to identify employers at each worksite who violate the law and ordinance due to a shortage of officers. A practical solution is to raise the knowledge level of employees in small companies with regard to health and to inform them of their right to receive healthcare services.

The Ministry of Health, Labour and Welfare promotes the “National Health Promotion Movement in the 21st Century (Health Japan 21),” which aims to reduce the number of premature deaths, prolong healthy years of life, and improve people’s quality of life since 2000.³⁹ In 2013, this campaign was updated as ‘Health Japan 21 (the second term).’ In this program, primary and secondary prevention of NCDs is defined as a major goal, which ultimately aims to reduce gaps in health status among the Japanese population. Concerning CVD, one goal is to decrease the age-adjusted mortality due to stroke and CAD; this may be successfully accomplished by controlling major risk factors, including HTN, dyslipidemia, DM, and smoking. A 4-mmHg reduction in the mean systolic BP of the total population may be considered a quality indicator for controlling HTN, which plays a key role in reducing CVD. This decrease is expected to be accomplished by reducing salt intake, obesity, and high-risk drinking while increasing the intake of vegetables and fruits, PA (by increasing the daily number of steps) and medical treatment of individuals with HTN. Except for medication, most methods for decreasing BP consist of lifestyle modifications. As noted, some high-risk individuals may receive health guidance through MetS screening; however, it is more difficult to manage the majority of the population without MetS.

Therefore, a ‘population strategy,’ such as that pioneered by Geoffrey Rose^{34,15} and presented here, offers a potential approach to overcoming the challenges arising from the low rates of MetS screening and poor health of workers in small-scale companies. Further, this strategy serves to promote and support the goals of Health Japan 21. Clearly, the effectiveness of activities conducted in a high-risk strategy, such as providing health guidance to improve MetS, may also be strengthened and broadly supported by a population strategy. Therefore, implementing a combination of high-risk and population strategies in the workplace may be effective in improving lifestyles and controlling CVD risk factors in the

working population. However, although practical methods, such as MetS screening, for a high-risk strategy exist, pragmatic approaches to a population strategy are still under development in Japan.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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REFERENCES

- Ministry of Health, Welfare and Labour. 2010 comprehensive survey of living conditions of the people on health and welfare. Tokyo Health and Welfare Statistics Association. 2012. <http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa10/> (in Japanese).
- <http://law.e-gov.go.jp/htmldata/S47/S47HO057.html> (in Japanese).
- <http://law.e-gov.go.jp/htmldata/S47/S47F04101000032.html> (in Japanese).
- Sakurai H. Occupational safety and health in Japan: current situations and the future. *Ind Health*. 2012;50:253-260.
- Ikeda N, Saito E, Kondo N, et al. What has made the population of Japan healthy? *Lancet*. 2011;378:1094-1105.
- Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. *Int J Epidemiol*. 2000;29:837-844.
- Lifestyle-Related Disease Control Bureau of the Ministry of Health, Labour and Welfare. Kokumin Eiyo no Genjyo 1998 [The National Nutrition Survey, Japan]. Tokyo: Daiichi Shuppan. 2000.
- Shimamoto T, Komachi Y, Inada H, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation*. 1989;79:503-515.
- Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H, Japan Arteriosclerosis Longitudinal Study Group. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events - the JALS-ECC -. *Circ J*. 2010;74:1346-1356.
- NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J*. 2006;70:1249-1255.
- Hirobe K, Terai T, Fujioka S, Goto K, Dohi S. 3M-Study Project Committee of the Japan Association of Occupational Physicians "San-yu-kai"; Morbidity of Myocardial Infarction Multi-center Study in Japan (3M Study): study design and event rates for myocardial infarction and coronary death by age category in Japanese workers. *Circ J*. 2005;69:767-773.
- Maruyama K, Hirobe K, Noda H, Iso H, Dohi S, Terai T, Fujioka S, Goto K, Horie S, Nakano S. Associations between blood lipid profiles and risk of myocardial infarction among Japanese male workers: 3M Study. *J Atheroscler Thromb*. 2009;16:714-721.
- Noda H, Maruyama K, Iso H, Dohi S, Terai T, Fujioka S, Goto K, Horie S, Nakano S, Hirobe K. 3M Study Project Committee of the Japan Association of Occupational Physicians "San-yu-kai"; Prediction of myocardial infarction using coronary risk scores among Japanese male workers: 3M Study. *J Atheroscler Thromb*. 2010;17:452-459.
- Rose G. The Strategy of Preventive Medicine. Oxford: Oxford University Press. 1992.
- Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 2001;30:427-432.
- Okamura T, Tanaka T, Sabazono A, et al. The high-risk and population strategy for occupational health promotion (HIPOP-OHP) study: study design and cardiovascular risk factors at the baseline survey. *J Hum Hypertens*. 2004;18:475-485.
- Okamura T, Tanaka T, Takebayashi T, et al. Methodological issues for a large-scale intervention trial of lifestyle modification: Interim assessment of the high-risk and population strategy for occupational health promotion (HIPOP-OHP) study. *Environ Health Prev Med*. 2004;9:137-143.
- Tanaka T, Okamura T, Yamagata Z, et al. Awareness and treatment of hypertension and hypercholesterolemia in Japanese workers: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study. *Hypertens Res*. 2007;30:921-928.
- Kamon Y, Okamura T, Tanaka T, et al. Marital status and cardiovascular risk factors among middle-aged Japanese male workers: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study. *J Occup Health*. 2008;50:348-356.
- Tamura U, Tanaka T, Okamura T, et al. Changes in weight, cardiovascular risk factors and estimated risk of coronary heart disease following smoking cessation in Japanese male workers: HIPOP-OHP study. *J Atheroscler Thromb*. 2010;17:12-20.
- Yoshita K, Tanaka T, Kikuchi Y, et al. The evaluation of materials to provide health-related information as a population strategy in the worksite: The high-risk and population strategy for occupational health promotion (HIPOP-OHP) study. *Environ Health Prev Med*. 2004;9:144-151.
- Naito M, Nakayama T, Okamura T, et al. Effect of a 4-year workplace-based physical activity intervention program on the blood lipid profiles of participating employees: the high-risk and population strategy for occupational health promotion (HIPOP-OHP) study. *Atherosclerosis*. 2008;197:784-790.
- Tanaka H, Yamato H, Tanaka T, et al. Effectiveness of a low-intensity intra-worksites intervention on smoking cessation in Japanese employees: a three-year intervention trial. *J Occup Health*. 2006;48:175-182.
- Hayashino Y, Fukuhara S, Okamura T, et al. A prospective study of passive smoking and risk of diabetes in a cohort of workers: the High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study. *Diabetes Care*. 2008;31:732-734.
- Funahashi T. Definition of metabolic syndrome in Japan—Concept and perspective. *Nippon Rinsho*. 2007;65(Suppl 7):84-90. (in Japanese).
- Kaplan NM. The deadly quartet: Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*. 1989;149:1514-1520.
- Kadota A, Hozawa A, Okamura T, et al. Relationship between metabolic risk factor clustering and cardiovascular mortality stratified by high blood glucose and obesity: NIPPON DATA90, 1990-2000. *Diabetes Care*. 2007;30:1533-1538.

28. Iso H, Sato S, Kitamura A, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. *Stroke*. 2007;38:1744–1751.
29. Hata J, Doi Y, Ninomiya T, et al. The effect of metabolic syndrome defined by various criteria on the development of ischemic stroke subtypes in a general Japanese population. *Atherosclerosis*. 2010;210:249–255.
30. Okamura T, Nakamura K, Kanda H, et al. Effect of combined cardiovascular risk factors on individual and population medical expenditures: a 10-year cohort study of national health insurance in a Japanese population. *Circ J*. 2007;71:807–813.
31. Okamura T, Kokubo Y, Watanabe M, et al. A revised definition of the metabolic syndrome predicts coronary artery disease and ischemic stroke after adjusting for low density lipoprotein cholesterol in a 13-year cohort study of Japanese: the Suita study. *Atherosclerosis*. 2011;217:201–206.
32. Miyake S. Long-term hypertension control in a community-comparison of stroke incidence and hypertension control between participants and nonparticipants in health examinations. *Nihon Koshu Eisei Zasshi*. 1993;40:606–623. (in Japanese).
33. Hirai T, Kusaka Y, Iki M, et al. Relationship of hypertension prevalence in companies to business type and scale—from an analysis of health examination results in Fukui prefecture. *Nihon Koshu Eisei Zasshi*. 1996;43:806–814. (in Japanese).
34. Yamataki H, Suwazono Y, Okubo Y, et al. Health status of workers in small and medium-sized companies as compared to large companies in Japan. *J Occup Health*. 2006;48:166–174.
35. Hoshuyama T, Hino Y, Kayashima K, et al. Inequality in the health status of workers in small-scale enterprises. *Occup Med (Lond)*. 2007;57:126–130.
36. Davey Smith G, Carroll D, Rankin S. Socio-economic differences in mortality: evidence from Glasgow graveyards. *BMJ*. 1992;305:1554–1557.
37. Kagamimori S, Gaina A, Nasermoaddeli A. Socioeconomic status and health in the Japanese population. *Soc Sci Med*. 2009;68:2152–2160.
38. Hirokawa K, Tsutsumi A, Kayaba K, the Jichi Medical Cohort study group. Mortality risks in relation to occupational category and position among the Japanese working population: the Jichi Medical School (JMS) cohort study. *BMJ Open*. 2013;3:e002690.
39. Sakurai H. Healthy Japan 21. *JMAJ*. 2003;46:47–49.