Ⅴ．研究成果の論文要旨

# Impact of Intima–Media Thickness Progression in the Common Carotid Arteries on the Risk of Incident Cardiovascular Disease in the Suita Study

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***Background***—No prospective study of the relationship between intima–media thickness (IMT) progression and incident cardiovascular disease (CVD) has been performed.

***Methods and Results***—We studied 4724 participants (mean age: 59.7±11.9 years; without CVD at the baseline) who had carotid ultrasonographic measurement of IMT on both sides of the entire carotid artery area (ie, the entire scanned common carotid artery [CCA], carotid artery bulb, internal carotid artery, and external carotid artery areas for both sides) between April 1994 and August 2001. Carotid ultrasonographic follow-up was performed every 2 years between April 1994 and March 2005 in 2722 of these participants, newly revealing 193 CCA plaques (maximum IMT in the CCA >1.1 mm). We followed up for incident CVD until December 2013. Statistical analyses were performed using a Cox proportional hazards regression model, evaluated using C statistics, and net reclassification improvement. During the 59 909 person-years of follow-up, we observed 221 strokes and 154 coronary heart disease events. CCA plaque and maximum IMT in the whole carotid artery area >1.7 mm were risk factors for CVD. CCA plaque presented an increased risk of CVD based on C statistics and the reclassification improvement of the current risk prediction model. After adding the new incident CCA plaques, during the 23 702 person-years of follow-up, 69 strokes and 43 coronary heart disease events occurred. The adjusted hazard ratios for incident CCA plaque were 1.95 (95% confidence interval, 1.14–3.30) in CVD and 2.01 (95% confidence interval, 1.01–3.99) in stroke.

***Conclusions***—Maximum IMT in the CCA contributed significantly but modestly to the predictive power of incident CVD used in calculating traditional risk factors. This study provides the first demonstration that new progression of incident CCA plaque is a CVD risk. (***J Am Heart Assoc.*** 2018;7:e007720. DOI: 10.1161/JAHA.117.007720.)

***Key Words:*** atherosclerosis • cardiovascular disease • carotid intima–media thickness • epidemiology • progression of carotid atherosclerosis • prospective cohort study

The carotid intima–media thickness (IMT) is a noninvasive intermediate marker that can be used for the prediction of stroke[1] and coronary heart disease (CHD).[2,3] The carotid IMT is also a surrogate marker for cardiovascular

risk factors[4] and atherosclerosis.[5,6] For preventive medicine, it would be useful to determine whether carotid IMT can be used to supplement traditional cardiovascular risks to increase the probability of predicting cardiovascular disease (CVD). The ARIC (Atherosclerosis Risk in Communities) study showed that adding the carotid IMT to traditional risk factors improved CHD risk prediction.[2] In the Framingham Offspring Study, maximum internal carotid artery (ICA) IMT and mean common carotid artery (CCA) IMT both predicted CVD outcomes, but only maximum ICA IMT slightly but significantly improved the classification of risk of CVD.[7] In contrast, carotid IMT did not consistently improve the risk classification of individuals in a general[8] or hypertensive population[9] in meta-analyses, although carotid IMT was predictive of CVD events. These inconsistent results may have been due to the use of the mean or maximum IMT or to differences in age range, ethnicity, and background of participants, such as the presence of hypertension between studies.

# Longitudinal Trajectories of Fasting Plasma Glucose and Risks of Cardiovascular Diseases in Middle Age to Elderly People Within the General Japanese Population: The Suita Study

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***Background***—Few previous studies used information on changes in fasting plasma glucose (FPG) assessed at multiple points in time in relationship to cardiovascular disease (CVD) incidence. The present study aimed to identify subgroups of FPG trajectories with assessing CVD incidence.

***Methods and Results***—The present study was based on the Suita study, a population-based cohort study in Japan. The primary outcome was incidence of the first CVD events consisting of stroke and coronary heart diseases between 1989 and 2013. The main exposure was FPG assessed every 2 years. We used joint latent class mixed models to derive FPG trajectories over time while evaluating cumulative incidence of CVD, and categorized participants into several subgroups based on those trajectories and cumulative incidence. We observed 356 and 243 CVD events during the median follow-up of 17.2 and 20.2 years among 3120 men and 3482 women, respectively. The joint latent mixed models found 3 subgroups in men and 2 subgroups in women. Of the 3 subgroups in men, 1 subgroup had FPG levels that increased sharply (96.5–205.0 mg/dL from aged 40 to 80 years) and higher CVD cumulative incidence. Of the 2 subgroups in women, 1 subgroup had FPG levels that increased sharply (97.7–190.5 mg/dL from aged 40 to 80 years) and tended to have slightly higher CVD incidence compared with the other subgroup.

***Conclusion***—It can be important to manage CVD risk factors especially for people whose FPG trajectories sharply increased to prevent CVD. (***J Am Heart Assoc***. 2019;8:e010628. DOI: 10.1161/JAHA.118.010628.)

**Key Words:** blood glucose trajectory • cardiovascular diseases • epidemiology

High blood glucose level can influence several etiologies of cardiovascular diseases (CVD) such as atherosclerosis and oxidative stress.[1–3] Previous studies showed that people with high blood glucose had higher CVD incidence than those without,[2,4–10] and our cohort, the Suita Study, showed similar results.[6–8]

Many previous studies did not investigate longitudinal changes (ie, trajectories) of fasting plasma glucose (FPG) in relationship to CVD incidence. In previous studies, FPG was usually used one point in time but not for multiple points in time (during the follow-up period), even though trajectories of

FPG may be useful to identify and prevent CVD incidence early. Types of FPG trajectories were significantly associated with incident myocardial infarction.[11] In this study, compared with people with a moderate-stable trajectory of FPG (4.9–5.1 mmol/L for 4 years), people with an elevated-stable trajectory of FPG (6.1–6.3 mmol/L for 4 years) developed more myocardial infarction (hazard ratio=1.53).[11]

However, in this previous study, the types of FPG trajectories were based only on FPG values assessed before the baseline, which encouraged us to use all of the available FPG values before CVD incidence to trajectory types. This can

# Choice reaction time and grip strength as predictors of cardiovascular mortality in middle-aged and elderly Japanese: from the Radiation Effects Research Foundation Adult Health study

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**Abstract**

**Background:** Cognitive function and physical function are important predictors of mortality.

**Aim:** To investigate whether or not reaction time (RT) as a cognitive function and grip strength (GS) as a physical function were associated, alone or in combination, with mortality from heart disease or stroke.

**Methods:** The subjects included 4901 Adult Health Study participants in Hiroshima who had undergone RT and GS measurements, were 35–74 years old at baseline (1970–1972) and were followed until the end of 2007.

**Results:** After adjustment for other potential risk factors, RT was positively and GS was negatively associated with mortality from both heart disease and stroke. These associations were persistent in the model when adjusting simultaneously for RT, GS and other factors, but hazard ratios were attenuated. When we evaluated the associations by baseline age and gender, we found the greater hazard ratios for RT in the younger cohort, but no clear modification by age for GS. The interaction between RT and GS was statistically significant ($P = 0.012$) for stroke mortality. In the stratified analyses divided using the age-specific median value of RT or GS, the estimated hazard ratio of stroke mortality for RT was significant in participants with weak or strong GS but greater in the former, and for GS, it was only significant in participants with slow RT.

**Conclusion:** RT and GS, alone and in combination, predicted heart disease and stroke mortalities. Interventions for both cognitive function and physical function may be beneficial for the prevention of cardiovascular disease mortality.

## Introduction

Cognitive function and physical function are important predictors of mortality. Reaction time (RT) is a measure

of processing speed,[1] and processing speed reflects cognitive function.[2] Using the Radiation Effects Research Foundation (RERF) Adult Health Study (AHS), which covered a wide age range of men and women over a period of 30 years, our previous study showed RT to be a strong and consistent predictor of mortality.[3] Some cohort studies found RT, including the digit symbol substitution test, to be related to cardiovascular disease (CVD) mortality[4,5] and CVD incidence.[6]

A meta-analysis by Cooper *et al.* found that grip strength (GS), which is a measure of physical function, is associated with all-cause mortality in younger, as well as older, community-dwelling populations.[7] The prospective Urban–Rural Epidemiology study, a large, longitudinal population study, showed that GS was inversely associated with all-cause mortality, cardiovascular

# Plasma Xanthine Oxidoreductase Activity as a Novel Biomarker of Metabolic Disorders in a General Population

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**Background:** Xanthine oxidoreductase (XOR) is an enzyme that catalyzes the formation of uric acid from hypoxanthine and xanthine, leading to an increase in superoxide and reactive oxygen species. Activation of XOR promotes oxidative stress-related tissue injury. We investigated the associations between metabolic parameters and plasma XOR activity measured by a sensitive and accurate assay using a combination of liquid chromatography and triple quadrupole mass spectrometry to detect $[^{13}C_2,^{15}N_2]$-uric acid using $[^{13}C_2,^{15}N_2]$-xanthine as a substrate.

**Methods and Results:** A total of 627 Japanese subjects (M/F, 292/335) from the Tanno-Sobetsu Study, a population-based cohort, were recruited. Plasma XOR activity was significantly higher in males than in females, and habitual smoking was associated with elevation of activity. Plasma XOR activity was positively correlated with body mass index (BMI; r=0.323, P<0.001), waist circumference, blood pressure, and levels of liver enzymes including alanine transaminase (r=0.694, P<0.001), uric acid (r=0.249, P<0.001), triglycerides (r=0.312, P<0.001), hemoglobin A1c, fasting glucose, insulin and HOMA-R (r=0.238, P<0.001) as a marker of insulin resistance and was negatively correlated with high-density lipoprotein cholesterol level. On stepwise and multivariate regression analyses, BMI, smoking and levels of alanine transaminase, uric acid, triglycerides and HOMA-R were independent predictors of plasma XOR activity after adjustment for age and gender.

**Conclusions:** Plasma XOR activity is a novel biomarker of metabolic disorders in a general population.

**Key Words:** Insulin resistance; Liver dysfunction; Obesity; Smoking; Uric acid

ric acid is the end product of purine metabolism in higher primates, including humans.[1] Hyperuricemia is closely associated with visceral fat accumulation[2,3] and various metabolic disorders conceptualized as metabolic syndrome, such as glucose intolerance, elevated blood pressure, dyslipidemia and atherosclerotic cardiovascular disease.[4] Therefore, elevation of uric acid has been thought to be a possible marker of metabolic and cardiovascular diseases. It has not, however, necessarily been proven that the risk of cardiovascular events can be decreased by reduction of uric acid.[5-7]

Xanthine oxidoreductase (XOR) is an enzyme that catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid in the purine metabolism pathway.[8] In mammals, XOR can convert 2 different forms, xanthine dehydrogenase (XDH) and xanthine oxidase (XO). XDH reduces $NAD^+$ to NADH, whereas XO consumes oxygen to produce superoxide. XOR activity implies the total activity of both forms.[9] XOR exists as the XDH form in several tissues, including the liver, intestine and other organs, and leaks into the blood and consequently converts to the XO form.[10,11] Since activation of XOR promotes a resultant increase in superoxide,[9] XOR is recognized as a significant source of reactive oxygen species, contributing to the development of oxidative stress-related tissue injury.[12-14] It has, however, been difficult to accurately measure plasma XOR activity in humans because the activity is much lower in humans than in animals.[15] Therefore, the relationship between plasma XOR activity and metabolic phenotype in humans remains to be elucidated.

Recently, a novel, sensitive and accurate assay for plasma XOR activity in humans has been established using a combination of liquid chromatography and triple quadrupole mass spectrometry (LC/TQMS) to detect $[^{13}C_2,^{15}N_2]$-uric

# Water intake from foods and beverages and risk of mortality from CVD: the Japan Collaborative Cohort (JACC) Study

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## Abstract

*Objective:* To examine the association of water intake with risk of mortality from CVD.

*Design:* Prospective cohort study.

*Setting/Subjects:* A total of 22 939 men and 35 362 women aged 40–79 years enrolled in the Japan Collaborative Cohort (JACC) Study with available data regarding water intake from foods and beverages. The underlying causes of death were determined based on the International Classification of Diseases.

*Results:* During the median 19·1 years of follow-up, 1637 men and 1707 women died from CVD. There was an inverse trend between high water intake and risk of CVD in both sexes. Compared with participants in the lowest quintile of water intake, the multivariable-adjusted hazard ratios (95 % CI) for mortality from total CVD in the highest quintile of water intake were 0·88 (0·72, 1·07; *P* for trend = 0·03) in men and 0·79 (0·66, 0·95; *P* for trend = 0·10) in women. Those for CHD were 0·81 (0·54, 1·21; *P* for trend = 0·06) in men and 0·60 (0·39, 0·93; *P* for trend = 0·20) in women. Reduced risk of mortality from ischaemic stroke was also observed among women in the highest water intake quintile: 0·70 (0·47, 0·99; *P* for trend = 0·19). There was no association between water intake and mortality from haemorrhagic stroke in either sex.

*Conclusions:* Higher intake of fluids from foods and beverages was associated with reduced risk of cardiovascular mortality in both sexes and reduced risk of ischaemic stroke in women in Japan.

No one can deny how essential water is for life. The human body comprises about 60–75 % water by weight[1]. The biological importance of water in man includes its roles in skin moisture[2], thermoregulation[3], cognition enhancement[4], gastrointestinal function and nutrient absorption[5], renal filtration and urinary excretion of blood wastes[6] and cellular homeostasis via maintaining balanced water/mineral content in different body fluids[1].

The human consumption of fluids comes not only from plain water to quench thirst, but also some portion of our daily water intake comes from the moisture in foods and beverages. The proportion of plain water intake to total water intake differs among populations, depending on various factors such as sex, age, weight and climate[7–11]. However, the WHO recommends a daily water intake of 2·9 litres for men and 2·2 litres for women under standard conditions[12].

Evidence has been ranked from weak to strong regarding the association of good hydration with reduced risks of different chronic diseases including chronic kidney disease[13], CHD[14] and total mortality[15], and it was estimated that a 20 % loss of the body's water content can lead to death[16]. A specific importance of water is its impact on the cardiovascular system because water input/output regulates blood volume, which correlates with blood pressure and heart rate[6,17]. Moreover, it was shown in both normotensive and hypertensive individuals that water intake acutely increases the blood pressure while reducing the heart rate[17]. Those effects are caused by enhancing the sympathetic nervous system and

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# Associations between copper and zinc intakes from diet and mortality from cardiovascular disease in a large population-based prospective cohort study☆,☆☆

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## Abstract

Several studies have related cardiovascular disease (CVD) to serum concentrations of copper and zinc but not to their dietary intakes. We thought to examine the association between dietary intakes of copper and zinc with risk of mortality from CVD in a prospective study encompassing 58,646 healthy Japanese men and women aged 40-79 years. The intakes of copper and zinc were determined by a validated self-administered food frequency questionnaire, and their associations with risk of mortality from CVD were evaluated by Cox proportional hazard modelling. During 965, 970 person-years of follow-up between 1989-2009, we documented 3,388 CVD deaths [1,514 from stroke, 702 from coronary heart disease (CHD) and 1,172 from other CVD]. Copper intake was not associated with CHD mortality; however, the multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality from stroke, other CVD and total CVD in the highest versus the lowest quintiles of copper intake among men were 1.78 (1.16-2.77; P-trend=0.007), 1.61 (1.01-2.81; P-trend =0.03) and 1.63 (1.21-2.33; P-trend=0.001), respectively, and those among women were 1.49 (1.00-2.19; P-trend=0.04), 1.59 (1.09-2.55; P-trend =0.02) and 1.36 (1.06-1.69; P-trend=0.01), respectively. Higher intakes of zinc was inversely associated with mortality from CHD in men; 0.68 (0.58-1.03; P-trend=0.05) but not women; 1.13 (0.71- 1.49; P-trend=0.61). No associations were observed with other mortality endpoints. In conclusion, dietary copper intake was positively associated with mortality from CVD in both genders; whereas, higher dietary zinc intake was inversely associated with mortality from CHD in men but not women.
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*Keywords:* Copper; Zinc; Stroke; Coronary heart disease; Cardiovascular diseases; Japanese

## 1. Introduction

A universal leading cause of death is cardiovascular disease (CVD) [1]. When compared with Western population, Japan has a consider-able very low prevalence of coronary heart disease (CHD) mortality but not stroke mortality [1].

The surge in CVD mortality has been attributed to environmental determinants including declined diet quality [2]. Lifestyle

Applied nutritional investigation

# Dietary intakes of fat soluble vitamins as predictors of mortality from heart failure in a large prospective cohort study

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## A R T I C L E   I N F O

## A B S T R A C T

*Objectives:* A few reports have investigated the association of dietary vitamin intakes with risk of heart failure in Asia. Therefore, we examined the relation between dietary intakes of fat-soluble vitamins A, K, E, and D and mortality from heart failure in the Japanese population.
*Methods:* A total of 23 099 men and 35 597 women ages 40 to 79 y participated in the Japan Collaborative Cohort Study and completed a food frequency questionnaire from which dietary intakes of vitamins A, K, E, and D were calculated. The Cox proportional hazard model was used to estimate the sex-specific risks of heart failure mortality according to increasing quintiles of fat-soluble vitamin intakes.
*Results:* During the median 19.3 y follow-up period, there were 567 deaths from heart failure (240 men, 327 women). Dietary vitamin A intake showed no association with heart failure mortality in both sexes; however, the reduced risk was observed in women but not in men with dietary intakes of vitamins K, E, and D. The multivariable hazard ratios (95% confidence interval) in the highest versus the lowest intake quintiles among women were 0.63 (0.45–0.87; *P* for trend = 0.006) for vitamin K, 0.55 (0.36–0.78; *P* for trend = 0.006) for vitamin E, and 0.66 (0.48–0.93; *P* for trend = 0.01) for vitamin D. The association for each vitamin was slightly attenuated but remained statistically significant after mutual adjustment for intakes of the other vitamins.
*Conclusions:* High dietary intakes of fat-soluble vitamins K, E, and D were associated with a reduced risk of heart failure mortality in Japanese women but not men.

## Introduction

Heart failure is a complex syndrome that stands on the activation of numerous biological mechanisms that follow or coincide with myocardial injury and lead to inadequate systematic perfusion [1]. In developed countries with a high proportion of aging population, such as in Japan, heart failure is a notable public health burden [2]. Intakes of seafood and fish [3,4], fermented soybeans [5], and fruits and vegetables [5,6] have been associated with a reduced risk of heart failure. In the Japanese diet, seafood and fish are the main dietary contributors of vitamin D [7], natto (i.e., fermented soybeans) is a major source of vitamin K [8], and vitamins A and E are mainly provided by the consumption of fruits and vegetables [9]. Whether the observed reduced risks with higher intakes of these foods are attributed to the effect of their content of fat-soluble vitamins (i.e., A, K, E, and D) remains unclear.

Dietary antioxidant capacity was inversely associated with the risk of cardiovascular diseases including heart failure [10]. However, the association between dietary intakes of vitamins A and E and cardiovascular mortality is questionable [11–13].

# Cardiovascular disease mortality in relation to physical activity during adolescence and adulthood in Japan: Does school-based sport club participation matter?

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## ARTICLE INFO

## ABSTRACT

We examined potential associations of sport club participation during adolescence and sports-related physical activity during adulthood with mortality from cardiovascular diseases (CVD) in a Japanese population. Between 1988 and 1990, 29,526 men and 41,043 women aged 40–79 years responded to a questionnaire including questions about the frequency of sports participation at baseline and sport club participation during junior/senior high school. Subjects were followed-up until the end of 2009, and 4230 cardiovascular deaths (870 CHD, 1859 stroke) were identified. Cox proportional-hazard regression models were used to estimate hazard ratios (HR). During the first-two thirds of the follow-up – where the proportional hazards assumption was met – the multivariate-adjusted HR (95% confidence interval) for total CVD mortality was 0.77 (0.61–0.98) among men and 0.82 (0.61–1.10) among women who were physically active at baseline ($\geq 5$ h/week versus 1–2 h/week). The corresponding HRs for coronary heart disease (CHD) mortality were 0.65 (0.39–1.07) and 0.40 (0.17–0.91), respectively. The combined associations of sports participation during adulthood and adolescence were also examined. Among men who participated in sports for $\geq 5$ h/week at baseline, the multivariate-adjusted HR for those who also engaged in sport club activities during adolescence was 0.89 (0.61–1.30) for total CVD mortality and 0.24 (0.08–0.71) for CHD mortality when compared to non-participants. Among women, no statistically significant differences were found between sport club participants and non-participants. In conclusion, participating in sport clubs during adolescence might lead to a more pronounced risk-reduction for CHD mortality among men who also participate in sport activities during adulthood.

## 1. Introduction

Taking part in cultural or sport club activities during junior/senior high school years is an integral part of Japanese culture. Previous studies reported that participating in school-based organized sport activities was associated with a favorable cardiovascular risk profile in Japanese adolescents, including elevated HDL-cholesterol and adiponectin levels, lower total cholesterol and triglyceride levels, decreased insulin resistance, lower blood pressure, lower body fat percentage, and was negatively associated with smoking and alcohol consumption

(Yoshinaga et al., 2011; Kawabe et al., 2000; Takasaki, 2005; Takakura, 2015). Cardiovascular risk factors and risk factor clustering tracking from childhood to adulthood was found to affect the risk of CVD morbidity and mortality in later years (Kemper et al., 1990; Webber et al., 1991; Chen and Wang, 2008; Toschke et al., 2010; Juhola et al., 2011; Joshi et al., 2014; Simmonds et al., 2016; Andersen et al., 2004; Camhi and Katzmarzyk, 2010; Baker et al., 2007; Morrison et al., 2012a; Morrison et al., 2012b; Llewellyn et al., 2016). Moderate to vigorous physical activity during adulthood was inversely associated with CVD morbidity and mortality due to improved lipid profile and

# Television viewing time, walking time, and risk of type 2 diabetes in Japanese men and women: The Japan Collaborative Cohort Study

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## ARTICLE INFO

## ABSTRACT

We examined the effect of television viewing and walking on the risk of type 2 diabetes among an Asian population. A total of 25,240 participants (9786 men and 15,454 women) aged 40–79 years, with no history of diabetes, stroke, coronary heart disease, or cancer at the baseline (1988–1990) and who have completed the 5-year follow-up questionnaire were included. During the 5-year follow-up, 778 new cases of type 2 diabetes were reported (397 men and 381 women). Television viewing time was positively associated with risk of type 2 diabetes (p for trend = 0.01). The multivariable OR (95% CI) for ≥5 h/day versus < 2 h/day television viewing was 1.51 (1.03–2.19) in women and 1.06 (0.71–1.59) in men (p for interaction = 0.82). Walking time was inversely associated with type 2 diabetes risk in a fully adjusted model (p for trend = 0.02). The multivariable OR for type 2 diabetes of ≥1 h/day walking time was 0.87 (0.71–1.06) compared with 0.5 h/day walking time. The inverse association was found in men (p for trend = 0.02), but not in women (p for trend = 0.38) (p for interaction = 0.36). The multivariable OR for type 2 diabetes of < 5 h/day television viewing and ≥1 h/day walking times was 0.72 (0.55–0.94) in fully adjusted model compared with ≥5 h/day television viewing and < 1 h/day walking times. Limiting television viewing time and increasing walking time may reduce risk of type 2 diabetes among Japanese.

## 1. Introduction

In 2014, the number of adults with diabetes in the world has reached 422 million (World Health Organization, 2016). Based on a patient survey conducted in Japan, the estimated number of patients with diabetes has increased from 2.12 million in 1999 to 3.17 million in 2014 (Ministry of Health, Labour and Welfare, 2014).

Several previous prospective cohort studies conducted among American (Hu et al., 2001, 2003; Krishnan et al., 2009; Joseph et al., 2016) and German (Ford et al., 2010) men and women and a meta-analysis (Grøntved and Hu, 2011) reported that prolonged television viewing, a common sedentary behavior, is associated with increased risk of type 2 diabetes. This meta-analysis of 4 prospective cohort studies showed that every 2 h increment in television viewing time per day was associated with 20% increase in type 2 diabetes risk (Grøntved and

Hu, 2011). In Japan, the average daily television viewing time spent in 2010 was approximately 3–4 h (Kobayashi et al., 2011). Although television viewing is a common daily sedentary behavior, few prospective studies have examined the effect of time spent viewing television on the risk of type 2 diabetes among the Asian populations. Japanese and East Asians have lower body mass index than do Caucasians (Yatsuya et al., 2014). Nevertheless, compared with Caucasians, Japanese are predisposed toward type 2 diabetes due to their lower capacity for insulin secretion (Kodama et al., 2013).

Meanwhile, a growing body of studies has shown that physical activity is an effective and modifiable lifestyle factor that can prevent the occurrence of type 2 diabetes. A meta-analysis has shown that participants who walked regularly had 15% reduced type 2 diabetes risk compared with those who spent almost no time walking (Aune et al., 2015). However, some Japanese studies reported the inconsistent

# Dietary Antioxidant Micronutrients and All-Cause Mortality: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk

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## ABSTRACT

**Background:** Oxidative stress, the imbalance between pro- and antioxidants, has been implicated in the etiology and pathophysiology of the incidence and mortality of many diseases. We aim to investigate the relations of dietary intakes of vitamin C and E and main carotenoids with all-cause mortality in Japanese men and women.

**Methods:** The Japan Collaborative Cohort Study for Evaluation of Cancer Risk had 22,795 men and 35,539 women, aged 40–79 years at baseline (1988–1990), who completed a valid food frequency questionnaire and were followed up to the end of 2009.

**Results:** There were 6,179 deaths in men and 5,355 deaths in women during the median follow-up of 18.9 years for men and 19.4 years for women. Multivariate hazard ratios for the highest versus lowest quintile intakes in women were 0.83 (95% confidence interval [CI], 0.76–0.90; *P* for trend < 0.0001) for vitamin C, 0.85 (95% CI, 0.78–0.93; *P* for trend < 0.0001) for vitamin E, 0.88 (95% CI, 0.81–0.96; *P* for trend = 0.0006) for *β*-carotene, and 0.90 (95% CI, 0.82–0.98; *P* for trend = 0.0002) for *β*-cryptoxanthin. The joint effect of any two of these highly correlated micronutrients showed significant 12–17% reductions in risk in the high-intake group compared with the low-intake group in women. These significant associations were also observed in the highest quintile intakes of vitamin C, vitamin E, and *β*-carotene in female non-smokers but were not observed in female smokers, male smokers, and non-smokers.

**Conclusions:** Higher dietary intakes of antioxidant vitamins may reduce the risk of all-cause mortality in middle-aged Japanese women, especially female non-smokers.

**Key words:** dietary antioxidants; carotenoids; vitamin C; vitamin E; all-cause mortality

## INTRODUCTION

Oxidative stress, the imbalance between pro- and antioxidants, has been implicated in the etiology, pathophysiology, and increased incidence of many chronic diseases and mortality.[1,2] Vitamin C, vitamin E, and carotenoids are essential antioxidants in diet and may prevent oxidative damages by free radicals.[3–5] Observational studies in populations reported that higher dietary intake of vitamin C,[6–9] vitamin E,[10] and carotenoids,[7,8,10] or greater balance of antioxidant scores[4,11] have been associated with decreased risk of all-cause mortality; however, these relationships were not confirmed in many studies for individual dietary nutrients, such as vitamin C,[2,5,10,12,13] vitamin E,[5,7,12,13] and *β*-carotene.[5,12,13] In addition, smokers can be at risk for anti-/ pro-oxidant imbalances of body tissues due to the excessive oxidants and free radicals from cigarette smoke.[11]

Fewer studies have been carried out to measure the association between antioxidants and the risk of all-cause mortality in Asian populations.[9] Antioxidants and other micronutrients are rich in Japanese foods, such as fruits, vegetables, and green tea.[14] The JACC Study reported that higher dietary intake of potatoes, spinach, or garland chrysanthemums was associated with reduced risk of all-cause mortality in both men and women, and that higher intake of carrot or pumpkin was associated with reduced risk of all-cause mortality in women.[15] Favorable effects of fruits and vegetables could in part be driven by high antioxidant nutrients.[16] The JACC Study also reported inverse associations of dietary vitamin C and E intakes with mortality from cardiovascular disease (CVD).[14] Although that report did not include carotenoids, serum beta-carotene was associated with cancer and all-cause mortality in a subpopulation of the JACC Study.[17,18] In spite of these reports, the overall association

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# Fish Intake and Death From Pulmonary Embolisms Among Japanese Men and Women
## — The Japan Collaborative Cohort (JACC) Study —

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Akiko Tamakoshi, MD, PhD; JACC Study Group

**Background:** Numerous studies have reported the association of cardiovascular risk factors with pulmonary embolism (PE), but the association of dietary factors, especially fish intake, with the risk of PE has not been fully established.

**Methods and Results:** Using a prospective design, we studied the risk of PE mortality in relation to fish intake in 90,791 community-dwelling men and women in Japan aged 40–79 years. The hazard ratios (HRs) and 95% confidence intervals (CIs) for PE death were estimated using the Cox proportional hazards model. Compared with participants in the lowest fresh fish intake group (<1 time/month), the HRs (95% CIs) for PE death for those in the other intake groups were 0.35 (0.08–1.59) for 1–2 times/month, 0.19 (0.05–0.69) for 1–2 times/week, 0.20 (0.06–0.74) for 3–4 times/week, and 0.18 (0.05–0.66) for fish intake every day. In addition to these findings, compared with the participants in the lowest 10% of $\omega3$ polyunsaturated fatty acid intake, those in the other groups had a 60–76% lower risk of PE death.

**Conclusions:** Fresh fish intake, even 1–2 times/week, is associated with a lower risk of death from PE among Japanese men and women.

**Key Words:** Diet; Epidemiology; Prospective cohort study; Risk factors; Venous thromboembolism

P ulmonary embolism (PE) is a common clinical condition with considerable associated morbidity and mortality, especially in Europe and North America: reported incidence rates for PE range from 45 to 65 per 100,000 person-years.[1–4] Conversely, Asians have a strikingly lower prevalence of both deep venous thrombosis (DVT) and PE.[5,6] In Japan, although the annual incidence rate of PE was estimated to be 12.6 per 100,000 persons in 2011,[7] the number of patients with PE has increased 4.6-fold in the past 15 years.[7]

Dietary intake may be one plausible explanation for the differences in the morbidity and mortality rates of PE between Western countries and Japan. Previous epidemiological studies have shown that factor VIII coagulant activity (FVIIIc), von Willebrand factor (vWF), platelet aggregation, and homocysteine levels are associated with the incidence of DVT and PE,[8,9] and these factors may be affected by dietary intake.[10] In the Longitudinal Investigation of Thromboembolism Etiology (LITE) study of 14,962 middle-aged whites and blacks, red and processed meat and a Western diet pattern were positively associated with the incidence of venous thromboembolism (VTE), while consumption of 4 or more servings of fruit and vegetables per day, or at least 1 serving of fish per week, was associated with lower incidence of VTE.[11] Because the average fish intake among the Japanese is 3–4-fold higher than that of Americans,[12] the low mortality rate from PE in the Japanese population may be attributable to a high intake of dietary fish. No observational study, however, has reported an association between diet and PE among Asians.

We therefore sought to examine the associations between dietary intake of fish and PE death using data from the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC), a nationwide community-based follow-up study of cardiovascular disease with one of the largest subject cohorts in Asia. Our a priori hypothesis was that fish and/or $\omega3$ polyunsaturated fatty acid (PUFA) intake would be associated with a lower risk of PE death within a population with a high mean fish intake.

# Brief Reports

# Relationship Between Dietary Vitamin D and Deaths From Stroke and Coronary Heart Disease
## The Japan Collaborative Cohort Study

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***Background and Purpose***—There is growing evidence about the importance of vitamin D for cardiovascular health. Therefore, we examined the relationship between dietary vitamin D intake and risk of mortality from stroke and coronary heart disease in Japanese population.

***Methods***—A prospective study encompassing 58 646 healthy Japanese adults (23 099 men and 35 547 women) aged of 40 to 79 years in whom dietary vitamin D intake was determined via a self-administered food frequency questionnaire. The median follow-up period was 19.3 years (1989–2009). The hazard ratios and 95% confidence intervals of mortality were calculated using categories of vitamin D intake.

***Results***—During 965 970 person-years of follow-up, 1514 stroke and 702 coronary heart disease deaths were documented. Vitamin D intake was inversely associated with risk of mortality from total stroke especially intraparenchymal hemorrhage but not from coronary heart disease; the multivariable hazard ratios (95% confidence intervals) for the highest (≥440 IU/d) versus lowest (<110 IU/D) categories of vitamin D intake were 0.70 (0.54–0.91; *P* for trend=0.04) for total stroke and 0.66 (0.46–0.96; *P* for trend=0.04) for intraparenchymal hemorrhage.

***Conclusions***—Dietary vitamin D intake seems to be inversely associated with mortality from stroke.   (***Stroke***. 2018;49:454-457. DOI: 10.1161/STROKEAHA.117.019417.)

**Key Words:** coronary disease ■ diet ■ stroke ■ surveys and questionnaires ■ vitamin D

A growing body of evidence indicates that vitamin D targets the cardiovascular system, exerting potential protection against neurovascular injury.[1] Specifically, low serum levels of vitamin D have been associated with an increased risk for stroke.[2,3] Although the major source of vitamin D for humans is exposure to sunlight, dietary and supplemental vitamin D are also essential for maintaining optimal vitamin D concentrations in the body.[1] Despite the evident association between serum vitamin D levels and risk of cardiovascular disease (CVD),[2,3] studies investigating the relationship between dietary vitamin D intake and risk of CVD are scarce and shown inconsistent results; no association in both sexes,[4] inverse associations in both sexes,[5,6] and inverse association in men but not women.[7] In particular, these relationships have not been examined for the Japanese population; therefore, we examined the relationship between dietary vitamin D intake and risk of mortality from stroke, stroke types, and coronary heart disease (CHD) in a large population-based Japanese study: The JACC (Japan Collaborative Cohort) Study.

## Subjects and Methods

To investigate factors related to cancer and CVD, 24 institutions participated in a multicenter collaborative study; the JACC Study that was launched at 1988 to 1990. The sampling methods and protocols of the JACC Study have been described in detail elsewhere.[8] In brief, recruitment of 110 585 inhabitants of 45 communities across Japan and aged 40 to 79 years was done by investigators who were responsible for conducting the cohort in that community. Informed consent was obtained from participants or community leaders, and the ethical committees of Hokkaido University and Osaka University approved the protocol of this study. Data, analytic methods, and study materials are available to other researchers at http://publichealth.med. hokudai.ac.jp/jacc/. Because the calculation of dietary nutrients was not conducted for participants with missing information for >4 food items, including rice or miso soup, a total of 58 646 individuals were eligible for the current analysis (Figure I in the online-only Data Supplement). At baseline, participants completed a self-administered questionnaire about their demographic characteristics and lifestyles and included a food frequency questionnaire inquiring about their usual frequency of food intake for the past year.[8] Dietary (not supplementary) vitamin D intake was calculated by multiplying the participants' frequency scores by the vitamin D content of each food

# "Ikigai", Subjective Wellbeing, as a Modifier of the Parity-Cardiovascular Mortality Association

## — The Japan Collaborative Cohort Study —

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Akiko Tamakoshi, MD, PhD; Hiroyasu Iso, MD, PhD

**Background:** Nulliparity is associated with an excess risk of cardiovascular disease (CVD). "Ikigai", subjective wellbeing in Japan, is associated with reduced risk of CVD. The impact of ikigai on the association between parity and the risk of CVD, however, has not been reported.

**Methods and Results:** A total of 39,870 Japanese women aged 40–79 years without a history of CVD, cancer or insufficient information at baseline in 1988–1990, were enrolled and followed until the end of 2009. They were categorized into 7 groups according to parity number 0–≥6. Using Cox regression hazard modeling, the associations between parity and mortality from stroke, coronary artery disease, and total CVD were investigated. During the follow-up period, 2,121 total CVD deaths were documented. No association was observed between parity and stroke and CVD mortality in women with ikigai, but there was an association in those without ikigai. The multivariable hazard ratios of stroke and total CVD mortality for nulliparous women without ikigai vs. those with 1 child were 1.87 (95% CI: 1.15–3.05) and 1.46 (95% CI: 1.07–2.01), respectively, and that for stroke mortality in high parity women without ikigai was 1.56 (95% CI: 1.00–2.45).

**Conclusions:** Nulliparous or high parity women without ikigai had higher mortality from stroke and/or total CVD, suggesting that ikigai attenuated the association between parity and CVD mortality in Japanese women.

**Key Words:** Cardiovascular disease; Ikigai; Mortality; Parity

ardiovascular disease (CVD) is a leading cause of mortality in both Western countries and in Japan. Reproductive factors are one of the important factors associated with the risk of CVD. In the Framingham Heart Study and the National Health and Nutrition Examination Survey National Epidemiologic Follow-up Study conducted in 1993, Ness et al reported that high parity, as compared with nulliparity, increased the mortality from coronary artery disease (CAD) and CVD.[1] In the American Cancer Society Cancer Prevention Survey II cohort study involving 585,445 subjects, Steenland et al showed that nulliparous women were at a higher risk for CVD than were parous women.[2] A study of 119,963 US women, however, reported no association between parity and the risk of CVD mortality.[3] A meta-analysis of 10 cohort studies in Western and Asian countries reported that parous women had a lower risk of CVD mortality than did nulliparous women.[4]

There is growing evidence that positive psychological factors are associated with lower risk of CVD mortality.[5–9] For example, Giltay et al reported that having high optimism resulted in a 77% reduction in CVD mortality as compared with having high pessimism, in a prospective population-based cohort study of 941 subjects in the Netherlands.[5] Similarly, several Japanese studies showed that having "ikigai", culturally defined as a comprehensive concept describing subjective wellbeing in Japan,[10] was associated with reduced risk of CVD incidence and mortality.[11–14] Ikigai means, briefly, something to live for, the joy and goal of living, a life worth living, and the happiness and benefit of being alive.[10–12]

Lifestyle behaviors, such as having habitual physical activity and not currently smoking, and socioeconomic factors such as higher education level, social support or networks were associated with lower CVD mortality.[15–19] Women may experience more of those factors through their

# Association between social participation and incident risk of functional disability in elderly Japanese: The Ohsaki Cohort 2006

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A B S T R A C T

Background: Although several longitudinal studies have examined the relationship between social participation and incident functional disability, the related mechanisms have remained unclear. The aim of this study was to examine the mechanisms linking social participation to incident functional disability.
Methods: We analyzed follow-up data for 11,992 older adults (≥65 years) participating in a community-based, prospective cohort study covering a 9-year period. At the baseline, the subjects were asked about three types of participation in community activities (volunteering, hobbies, and neighborhood associations) and the frequency of their participation. Data on incident functional disability were retrieved from the public Long-term Care Insurance database. The Cox model was used to estimate the multivariate-adjusted hazard ratios of incident functional disability. We then conducted mediation analysis to assess the magnitude of the mediating effect.
Results: Among 84,760 person-years of follow-up, there were 3,984 cases of incident functional disability. The hazard ratio was 0.79 (95% CI: 0.73-0.86) for participating in one type of activity, 0.82 (95% CI: 0.74-0.90) for two types of activity and 0.70 (95% CI: 0.64-0.77) for three types of activity in comparison with no participation in any activity. Among the estimated mediating effects, cognitive activity accounted for 9.3%, time spent walking for 8.3%, psychological state for 4.6%, and social support for 2.8% of the reduced risk of incident functional disability.
Conclusion: The results of this population-based cohort study indicate that cognitive activity and time spent walking are important mechanisms linking social participation to incident functional disability.

## 1. Introduction

As the number of older people requiring long-term care is increasing, prevention of functional disability is becoming a socially important issue [1]. For individuals as well as society as a whole, factors that can help to prevent functional disability are of interest. Social participation has been shown to be a factor that can help to protect against health problems (assessed in terms of mortality [2], morbidity [3] and self-reported health [4]), and may have beneficial effects in reducing the risk of functional disability.

Several longitudinal studies have examined the relationship between social participation and incident functional disability [5–7]. These showed that greater social participation was related to a lower risk of incident functional disability [5,6]. In terms of the type of social participation, the results for each of "hobby", "sports" and "volunteering" were consistent, but this was not the case for other types of

activity (e.g. political organizations or groups, industrial or trade associations, religious organizations or groups, citizen or consumer groups and senior citizen clubs) [6,7]. Although, overall, these longitudinal studies have indicated that social participation may help to reduce the risk of incident functional disability, more studies are needed to confirm these findings [5–7].

Moreover, no previous study has investigated the variables that link social participation to functional disability. Some physical and psychosocial pathways have been discussed in previous studies [5–7]. With regard to the physical pathway, physical activities inherent to social participation reinforce the motor function required to maintain functional independence. In terms of psychosocial pathway, social participation allows individuals to develop social relationships, which leads to acquisition of social support and recognition of social roles, and may even act as a buffer against stress. Previous studies have not addressed cognitive aspects of the relationship between social participation and

## ORIGINAL ARTICLE

# Changes in sleep duration and the risk of incident dementia in the elderly Japanese: the Ohsaki Cohort 2006 Study

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## Abstract

**Study Objectives:** To examine the association between changes in sleep duration and the risk of incident dementia in the elderly.

**Methods:** In 2006, we conducted a cohort study of 7422 disability-free Japanese individuals aged ≥65 years who lived in Ohsaki City, Japan. In both 1994 and 2006, the individual amount of sleep obtained was assessed using a self-reported questionnaire. Based on sleep duration at these two time points, participants were categorized into five groups according to the change in sleep duration. Data on incident dementia were retrieved from the public Long-term Care Insurance database, and the subjects were followed up for 5.7 years (between April 2007 and November 2012). The Cox proportional hazards model was used to estimate the multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident dementia.

**Results:** During 36 338 person-years of follow up, 688 cases of incident dementia were documented. Compared with subjects who had no change in sleep duration, the multivariate HRs (95% CIs) of incident dementia were 1.31 (1.07 to 1.60) for those whose sleep duration increased by 1 hr, and 2.01 (1.51 to 2.69) for an increase of ≥2 hr.

**Conclusions:** Increased sleep duration is associated with a significantly higher risk of incident dementia in the elderly. Future studies using well-validated measurements are needed to confirm the association between sleep and dementia.

### Statement of Significance

Previous studies have indicated that both long and short sleep duration are associated with a higher risk of cognitive impairment or incident dementia among the elderly. Only two previous studies have investigated the association between changes in sleep duration and incident dementia, but their results were inconsistent. Our present study, using data from a large-scale population-based cohort study, provided evidence that an increase rather than a decrease in sleep duration during a 12-year period was a risk factor of incident dementia, and that an increase in sleep duration was associated with a higher risk of dementia. Future studies employing objective measurements of sleep are needed to verify this association, and the underlying mechanisms should be examined.

**Key Words:** changes in sleep duration; incident dementia; aging; cohort study; Japanese population

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# Psychological distress and completed suicide in Japan: A comparison of the impact of moderate and severe psychological distress

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A B S T R A C T

It has already been established that severe psychological distress is a major risk factor for completed suicide. However, the impact (population attributable fraction; PAF) of moderate psychological distress on completed suicide has not been clarified. The present study investigated the association between various severities of psychological distress and completed suicide. We analyzed follow-up data covering a 7.3-year period (2006–2014) for 43,473 adults (aged ≥ 40 years) participating in a community-based, prospective cohort study. Psychological distress was measured using the K6 psychological distress scale at the baseline. Participants were classified into three groups according to their K6 score (low: 0–4; moderate: 5–12; severe: 13–24). Completed suicide was determined from a Japanese national database. The Cox model was used to estimate hazard ratios (HRs) for completed suicide. The PAFs of moderate and severe psychological distress for completed suicide were also estimated. The multivariate-adjusted HRs (95% confidence interval) for completed suicide were 2.37 (1.49–3.78) among participants with moderate psychological distress, and 4.16 (2.13–8.15) among those with severe psychological distress, relative to those with low psychological distress (P for trend < 0.001). The PAF of the moderate group for completed suicide was 26.8%, whereas that of the severe group was 10.9%. Not only severe but also moderate psychological distress was significantly associated with an increased risk of completed suicide. The PAF of moderate psychological distress for completed suicide was larger than that of severe psychological distress. Public health actions for suicide prevention should focus on moderate as well as severe psychological distress.

## 1. Introduction

The suicide rate in Japan (16.8 per 100,000 person-years in 2016) is among the highest in the world (Statistics and Information Department Minister's Secretariat Ministry of Health Labour and Welfare Japan, 2017). According to data from the World Health Organization (WHO) for the period 2013–2015, the suicide rate in Japan ranked sixth in the world, being especially high among the developed countries (World Health Organization, 2017). In fact in Japan, suicide is the second to fourth leading cause of death among middle-aged adults aged 40 to 64 years (Statistics and Information Department Minister's Secretariat Ministry of Health Labour and Welfare Japan, 2017). Thus, public health action for suicide prevention is an important issue in Japan.

It has been generally acknowledged that psychological illness including clinical depression is a major risk factor for completed suicide (Walker et al., 2015). Accordingly, public health action for suicide prevention has focused on individuals with severe psychological distress (Zalsman et al., 2016). Only one previous study has investigated the association between various severities of psychological distress and completed suicide in a general population (Bell et al., 2015). That study reported that not only severe but also moderate psychological distress was associated with an increased risk of completed suicide. Additionally, in the case of Japan, it has been reported that the prevalence of moderate psychological distress (23.1%) is approximately 7 times higher than that of severe psychological distress (3.5%) among adults aged 40 years and older (Ministry of Health, Labour and Welfare, Japan, 2017). Therefore, the population attributable fraction (PAF) of moderate psychological distress for completed suicide may be higher than that of severe psychological distress because the prevalence of the former is higher than that of the latter, even if the relative risk is lower for the former. Accordingly, the impact of moderate psychological distress on completed suicide may be larger than that of severe psychological distress. One previous systematic review has estimated the PAF of mental disorders (severe psychological

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# N-Terminal Pro-B-Type Natriuretic Peptide Is Not a Significant Predictor of Stroke Incidence After 5 Years
## — The Ohasama Study —

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Keiko Murakami, PhD; Ayako Matsuda, PhD; Azusa Hara, PhD; Taku Obara, PhD;
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Koichi Node, MD, PhD; Yutaka Imai, MD, PhD; Takayoshi Ohkubo, MD, PhD

***Background:*** N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been used for risk stratification in heart failure or acute coronary syndrome, but the beyond 5-year predictive value of NT-proBNP for stroke remains an unsettled issue in Asian patients. The aim of the present study was to clarify this point.

***Methods and Results:*** We followed 1,198 participants (33.4% men; mean age, 60.5±11.1 years old) in the Japanese general population for a median of 13.0 years. A first stroke occurred in 93 participants. Referencing previous reports, we stratified participants according to NT-proBNP 30.0, 55.0, and 125.0 pg/mL. Using the NT-proBNP <30.0 pg/mL group as a reference, adjusted HR for stroke (95% CI) in the NT-proBNP 30.0–54.9-pg/mL, 55.0–124.9-pg/mL, and ≥125.0-pg/mL groups were 1.92 (0.94–3.94), 1.77 (0.85–3.66), and 1.99 (0.86–4.61), respectively. With the maximum follow-up period set at 5 years, the hazard ratio of the NT-proBNP≥125.0-pg/mL group compared with the <30.0-pg/mL group increased significantly (HR, 4.51; 95% CI: 1.03–19.85). On extension of the maximum follow-up period, however, the association between NT-proBNP and stroke risk weakened.

***Conclusions:*** NT-proBNP was significantly associated with an elevated stroke risk. Given, however, that the predictive power decreased with the number of years after NT-proBNP measurement, NT-proBNP should be re-evaluated periodically in Asian patients.

**Key Words:** Epidemiology; N-terminal pro-B-type natriuretic peptide; Prevention; Stroke

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a stable N-terminal fragment of B-type natriuretic peptide (BNP) and is a useful tool for risk stratification in heart failure or acute coronary syndrome.[1–4] Moreover, NT-proBNP is considered a more sensitive marker of cardiac dysfunction than BNP.[5]

Although NT-proBNP has not been used for stroke risk stratification until now, a previous meta-analysis with a mean follow-up duration of 5 years reported the significance of NT-proBNP or BNP in stroke risk prediction.[6] An association of NT-proBNP or BNP with an increased risk for cardiovascular disease was significant even after

# Nocturnal blood pressure decline based on different time intervals and long-term cardiovascular risk: the Ohasama Study.

Satoh M, Asayama K, Kikuya M, Inoue R, Tsubota-Utsugi M, Obara T, Murakami K, Matsuda A, Murakami T, Nomura K, Metoki H, Imai Y, Ohkubo T.

## Abstract

A diminished nocturnal decline in blood pressure (BP) represents a risk factor for cardiovascular disease. To define daytime and nighttime ambulatory BP, clock time-dependent methods are used when information on diary-based sleeping time is unavailable. We aimed to compare fixed-clock intervals with diary records to identify nocturnal BP declines as a predictor of long-term cardiovascular risk among the general population. Data were obtained from 1714 participants with no history of cardiovascular disease in Ohasama, Japan (mean age, 60.6 years; 64.9% women). We defined extreme dippers, dippers, non-dippers, and risers as nocturnal systolic BP decline ≥20%, 10-19%. 0-9%, and <0%, respectively. Over a mean follow-up period of 17.0 years, 206 cardiovascular deaths occurred. Based on diary records, multivariable-adjusted hazard ratios (HRs) for cardiovascular death compared with dippers were 1.24 (95% confidence interval [CI], 0.82-1.87) in extreme dippers, 1.21 (0.87-1.69) in non-dippers, and the highest HR of 2.31 (1.47-3.62) was observed in risers. Using a standard fixed-clock interval (daytime 09:00-21:00; nighttime 01:00-06:00), a nighttime 2 h-early shifted fixed-clock (daytime 09:00-21:00; nighttime 23:00-04:00), or a nighttime 2 h-late shifted fixed-clock (daytime 09:00-21:00; nighttime 03:00-08:00), the HR (95%CI) in risers compared with dippers was 1.57 (1.08-2.27), 2.02 (1.33-3.05), or 1.29 (0.86-1.92), respectively. Although use of diary records remains preferable, the standard and nighttime 2 h-early shifted fixed-clock intervals appear feasible for population-based studies.

# Association between tooth loss and cognitive impairment in community-dwelling older Japanese adults: a 4-year prospective cohort study from the Ohasama study.

Saito S, Ohi T, Murakami T, Komiyama T, Miyoshi Y, Endo K, Satoh M, Asayama K, Inoue R, Kikuya M, Metoki H, Imai Y, Ohkubo T, Hattori Y.

## Abstract

**BACKGROUND:**

Numerous prospective studies have investigated the association between the number of remaining teeth and dementia or cognitive decline. However, no agreement has emerged on the association between tooth loss and cognitive impairment, possibly due to past studies differing in target groups and methodologies. We aimed to investigate the association between tooth loss, as evaluated through clinical oral examinations, and the development of cognitive impairment in community-dwelling older adults while considering baseline cognitive function.

**METHODS:**

This 4-year prospective cohort study followed 140 older adults (69.3% female) without cognitive impairment aged ≥65 years (mean age: 70.9 ± 4.3 years) living in the town of Ohasama, Iwate Prefecture, Japan. Cognitive function was evaluated with the Mini-Mental State Examination (MMSE) in baseline and follow-up surveys. Based on a baseline oral examination, the participants were divided into those with 0-9 teeth and those with ≥10 teeth. To investigate the association between tooth loss and cognitive impairment, we applied a multiple logistic regression analysis adjusted for age, sex, hypertension, diabetes, cerebrovascular/cardiovascular disease, hypercholesterolemia, depressive symptoms, body mass index, smoking status, drinking status, duration of education, and baseline MMSE score.

**RESULTS:**

In the 4 years after the baseline survey, 27 participants (19.3%) developed cognitive impairment (i.e., MMSE scores of ≤24). Multiple logistic regression analysis indicated that participants with 0-9 teeth were more likely to develop cognitive impairment than those with ≥10 teeth were (odds ratio: 3.31; 95% confidence interval: 1.07-10.2). Age, male gender, and baseline MMSE scores were also significantly associated with cognitive impairment.

**CONCLUSIONS:**

Tooth loss was independently associated with the development of cognitive impairment within 4 years among community-dwelling older adults. This finding corroborates the hypothesis that tooth loss may be a predictor or risk factor for cognitive decline.

# Evidence-based proposal for the number of ambulatory readings required for assessing blood pressure level in research settings: an analysis of the IDACO database.

Yang WY, Thijs L, Zhang ZY, Asayama K, Boggia J, Hansen TW, Ohkubo T, Jeppesen J, Stolarz-Skrzypek K, Malyutina S, Casiglia E, Nikitin Y, Li Y, Wang JG, Imai Y, Kawecka-Jaszcz K, O'Brien E, Staessen JA; International Database; on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators.

## Abstract

**BACKGROUND:**

Guidelines on the required number of ambulatory blood pressure (ABP) readings focus on individual patients. Clinical researchers often face the dilemma of applying recommendations and discarding potentially valuable information or accepting fewer readings.

**METHODS:**

Starting from ABP recordings with ≥30/≥10 awake/asleep readings in 4277 participants enrolled in eight population studies in the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO), we randomly selected a certain number of readings (from 30 to 1 awake and 10 to 1 asleep readings) at a time over 1000 bootstraps at each step. We evaluated: (i) concordance of the ABP level; (ii) consistency of the cross-classification based on office blood pressure and ABP; and (iii) accuracy in predicting cardiovascular complications. For each criterion, we fitted a regression line joining data points relating outcome to the number of readings covering the ranges of 30-20/10-7 for awake/asleep readings.

**RESULTS:**

Reducing readings widened the SD of the systolic/diastolic differences between full (reference) and selected recordings from 1.7/1.2 (30 readings) to 14.3/10.3 mm Hg (single reading) during wakefulness, and from 1.9/1.4 to 10.3/7.7 mm Hg during sleep; lowered the κ statistic from 0.94 to 0.63, and decreased the hazard ratio associated with 10/5 mm Hg increments in systolic/diastolic ABP from 1.21/1.14 to 1.06/1.04 during wakefulness and from 1.26/1.17 to 1.14/1.08 during sleep. The first data points falling off these regression lines during wakefulness/sleep corresponded to 8/3 and 8/4 readings for criteria (i) and (iii) and to 5 awake readings for criterion (ii).

**CONCLUSIONS:**

24-h ambulatory recordings with ≥8/≥4 awake/asleep readings yielded ABP levels similar to recordings including the guideline-recommended ≥20/≥7 readings. These criteria save valuable data in a research setting, but are not applicable to clinical practice.

## RESEARCH

# Metabolic syndrome is a risk factor for cancer mortality in the general Japanese population: the Jichi Medical School Cohort Study

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and Shizukiyo Ishikawa[1*]

## Abstract

**Background:** Metabolic syndrome (MetS) and cancer are major public health problems worldwide. The relationship between MetS and cancer death is of great interest. We examined the predictive value of MetS for cancer mortality in Japan.

**Methods:** Study participants included 4495 men and 7028 women aged 18–90 years who were registered between 1992 and 1995 as part of the Jichi Medical School Cohort Study. We used a definition of MetS modified for the Japanese population. The primary outcome was cancer mortality. Additionally, the relationship between MetS and cancer-type specific mortality was examined. Analyses were conducted with Cox's regression models adjusted for age, smoking status, alcohol drinking status, marital status, educational attainment, physical activity, occupational category, and menopausal status (only in women).

**Results:** During a mean follow-up of 18.5 years, 473 men and 297 women died from cancer. MetS was positively associated with cancer mortality in women (hazard ratio [HR], 1.69; 95% confidence interval [CI] 1.21–2.36), but not in men (HR, 1.21; 95% CI 0.90–1.62). Additionally, MetS was associated with a high risk of colorectal (HR, 3.48; 95% CI 1.68–7.22) and breast (HR, 11.90; 95% CI 2.25–62.84) cancer deaths in women.

**Conclusion:** MetS was a significant predictor of cancer mortality in women.

**Keywords:** Metabolic syndrome, Cohort studies, Neoplasm, Mortality, Japanese

## Background

Metabolic syndrome (MetS) is a disease characterized by a cluster of high blood glucose, dyslipidemia, obesity, and hypertension [1]. MetS is an important risk factor for not only cardiovascular diseases (CVD) but also the development of cancer [2, 3]. Accumulating evidence regarding the clinical value of MetS in estimating the risk of cancer has led to increased interest in the relationship between MetS and cancer.

Cancer remains a major cause of death worldwide, with 14.1 million new cases and 8.2 million deaths from cancer occurring annually [4]. Of note, cancer deaths in Japan have been gradually increasing and now constitute the leading cause of death in the country [5]. Each component of MetS, viz., obesity [6], hypertension [7], hyperglycemia [8–11], and dyslipidemia [12], independently increases the risk of cancer. However, it remains unclear whether there is a dose–response association between MetS components and cancer mortality. Despite substantial interest in the relationship between MetS and cancer

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# Journal of Epidemiology

# A Point System for Predicting 10-Year Risk of Developing Type 2 Diabetes Mellitus in Japanese Men: Aichi Workers' Cohort Study

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## ABSTRACT

**Background:** Relatively little evidence exists for type 2 diabetes mellitus (T2DM) prediction models from long-term follow-up studies in East Asians. This study aims to develop a point-based prediction model for 10-year risk of developing T2DM in middle-aged Japanese men.

**Methods:** We followed 3,540 male participants of Aichi Workers' Cohort Study, who were aged 35–64 years and were free of diabetes in 2002, until March 31, 2015. Baseline age, body mass index (BMI), smoking status, alcohol consumption, regular exercise, medication for dyslipidemia, diabetes family history, and blood levels of triglycerides (TG), high density lipoprotein cholesterol (HDLC) and fasting blood glucose (FBG) were examined using Cox proportional hazard model. Variables significantly associated with T2DM in univariable models were simultaneously entered in a multivariable model for determination of the final model using backward variable selection. Performance of an existing T2DM model when applied to the current dataset was compared to that obtained in the present study's model.

**Results:** During the median follow-up of 12.2 years, 342 incident T2DM cases were documented. The prediction system using points assigned to age, BMI, smoking status, diabetes family history, and TG and FBG showed reasonable discrimination (c-index: 0.77) and goodness-of-fit (Hosmer-Lemeshow test, $P = 0.22$). The present model outperformed the previous one in the present subjects.

**Conclusion:** The point system, once validated in the other populations, could be applied to middle-aged Japanese male workers to identify those at high risk of developing T2DM. In addition, further investigation is also required to examine whether the use of this system will reduce incidence.

**Key words:** type 2 diabetes mellitus; incidence; risk prediction; cohort study

## INTRODUCTION

The epidemic of diabetes is alarming worldwide.[1] Although both high-risk and population approaches are needed to tackle the epidemic, health check-ups are often implemented in community, worksite, or clinical settings in order to identify those at high risk.[2–4] However, it is not necessarily clear how to stratify individuals by disease risk. Although a number of type 2 diabetes mellitus (T2DM) prediction models have been reported,[5,6] there is a scarcity of evidence in East Asians, especially from long follow-up studies. The prevalence and extent of risk factors related to T2DM have been suggested to vary among ethnicities,[7–9] so it would be relevant to construct ethnicity-specific prediction model for T2DM. Among previous East Asian studies, some[10–13] implemented logistic regression analysis

without considering how predictors affect time to diabetes occurrence, and two studies[14,15] did not adopt lifestyles. From the viewpoint of primordial prevention, a long-term prediction model that included behavioral variables identified via long-term survival analysis would have significant importance. Long-term prediction model of T2DM using survival analysis has not been examined much in East Asians.[16–18] Therefore, the aim of the current study is to develop a point system to estimate 10-year risk of developing T2DM incidence in a middle-aged worksite-based male Japanese cohort, where health check-ups are conducted annually. The current study would add some to existing literature through the use of more recent data, more than 10-year follow-up time, and use of survival analysis. Moreover, we cross-validated the present model with an existing model[17] by comparing their performances when applied to the present population.

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**ORIGINAL ARTICLE**

# Association of gamma-glutamyl transferase and alanine aminotransferase with type 2 diabetes mellitus incidence in middle-aged Japanese men: 12-year follow up

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**ABSTRACT**

**Aims/Introduction:** To prospectively investigate whether simultaneous elevation of gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT) is associated with the increase of type 2 diabetes mellitus incidence independent of alcohol drinking, body mass index and triglycerides.

**Methods:** A total of 2,775 Japanese male workers who had no history of type 2 diabetes mellitus were followed. High GGT and ALT were defined as the top tertiles (GGT cutpoint: 49 IU/L, ALT cutpoint: 28 IU/L). Three groups were created using these dichotomized GGT and ALT cutpoints: both low, either high or both high. Multivariable Cox proportional hazards models were carried out adjusted for potential confounding factors.

**Results:** A total of 276 type 2 diabetes mellitus cases were identified during 12 years (27,040 person-years) of follow up. Participants with simultaneously elevated GGT and ALT had a significantly higher incidence of type 2 diabetes mellitus, even after adjustment for fasting insulin and fasting blood glucose compared with the group without GGT or ALT elevation. Similar associations were observed in non- or light-to-moderate alcohol drinkers, as well as in participants with normal weight. However, the association was weaker in participants with triglycerides <150 mg/dL. We then evaluated whether the addition of GGT and ALT would improve the prediction of type 2 diabetes mellitus incidence, and found that their inclusion significantly increased the C-statistic, net reclassification improvement and integrated discrimination improvement.

**Conclusions:** Simultaneous elevation of GGT and ALT was significantly associated with type 2 diabetes mellitus incidence, independent of potential confounding factors, including alcohol drinking and obesity, although the association might require concomitant elevation of triglycerides. Inclusion of GGT and ALT improved type 2 diabetes mellitus risk prediction.

## INTRODUCTION

The epidemic of diabetes mellitus is a serious global public health issue[1]. In Japan, the prevalence of diabetes mellitus is

expected to increase from 7.9 to 9.8% during the next two decades[2]. Understanding the pathophysiological pathways leading to type 2 diabetes mellitus would be important for planning effective and efficient prevention programs.

The liver plays an important role in the regulation of blood glucose levels, especially in the fasting state[3], and liver injury indicated by the elevation of blood alanine aminotransferase (ALT) or gamma-glutamyl transferase (GGT) levels has been

# The association between objective measures of residence and worksite neighborhood environment, and self-reported leisure-time physical activities: The Aichi Workers' Cohort Study

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## ARTICLE INFO

## ABSTRACT

The possible effects of a neighborhood's built environment on physical activity have not been studied in Asian countries as much as in Western countries. The present study cross-sectionally examined the relationship between geographic information system (GIS) measured residence and worksite neighborhood walkability, and the number of parks/green spaces and sports facilities within a 1 km radius of home and workplace, with self-reported leisure-time habitual (3–4 times per week or more) walking and moderate-to-vigorous intensity habitual exercise among local government workers aged 18 to 64 years living in an urban-suburban area of Aichi, Japan in 2013. A single-level binomial regression model was used to estimate the multivariable odds ratios (ORs) and 95% confidence intervals (95% CIs). Of the 1959 male and 884 female participants, 288 (15%) and 141 (16%) reported habitual walking, respectively, and 18% and 17% reported habitual exercise, respectively. Compared with women who resided in neighborhood with a walkability index of 4–30, those living in an area with that of 35–40 were significantly more likely to engage in leisure-time habitual exercise (multivariable OR: 1.70, 95% CI: 1.08–2.68). Marginally significant positive associations were found between leisure-time habitual exercise and the residential neighborhood's number of parks/green spaces among women, as well as the number of sports facilities among men. In conclusion, a residential neighborhood environment characterized by higher walkability may contribute to the initiation or maintenance of moderate-to-vigorous intensity leisure-time exercise among working women living in an urban-suburban area of Japan.

## 1. Introduction

Promoting physical activity is a public health priority worldwide, with major implications for the prevention of non-communicable diseases of populations (Kohl et al., 2012). There is growing interest in intervening environmental factors to promote physical activity within communities (Bauman et al., 2012), whereby studies conducted primarily in Western countries have indicated possible positive effects of neighborhood environment on physical activity (Astell-Burt et al., 2014; Kaczynski et al., 2008a, 2008b; Karusisi et al., 2013; Owen et al., 2007; Sallis et al., 2016; Sugiyama et al., 2014; Sundquist et al., 2011). For example, a multi-country study found that geographic information system (GIS) measures, such as the net residential density and the number of parks, were positively associated with the total amount of moderate-to-vigorous physical activity in adults living in urban cities (Sallis et al., 2016). Given that environment features, and social cultures and norms differ substantially between continents, the findings derived from Western countries are not necessarily applicable to Asian countries. To date, a limited number of studies have been carried out in Asian countries utilizing objectively measured environment