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ORIGINAL RESEARCH

Risk Classification for Metabolic Syndrome and the Incidence of Cardiovascular Disease in Japan With Low Prevalence of Obesity: A Pooled Analysis of 10 Prospective Cohort Studies

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BACKGROUND: It is uncertain whether risk classification under the nationwide program on screening and lifestyle modification for metabolic syndrome captures well high-risk individuals who could benefit from lifestyle interventions. We examined the validity of risk classification by linking the incidence of cardiovascular disease (CVD).

METHODS AND RESULTS: Individual-level data of 29 288 Japanese individuals aged 40 to 74 years without a history of CVD from 10 prospective cohort studies were used. Metabolic syndrome was defined as the presence of high abdominal obesity and/or overweight plus risk factors such as high blood pressure, high triglyceride or low high-density lipoprotein cholesterol levels, and high blood glucose levels. The risk categories for lifestyle intervention were information supply only, motivation-support intervention, and intensive support intervention. Sex- and age-specific hazard ratios and population attributable fractions of CVD, which were also further adjusted to consider non–high density lipoprotein cholesterol levels, were estimated with reference to nonobese/overweight individuals, using Cox proportional hazard regression. Since the reference category included those with risk factors, we set a supernormal group (nonobese/overweight with no risk factor) as another reference. We documented 1023 incident CVD cases (565 men and 458 women). The adjusted CVD risk was 60% to 70% higher in men and women aged 40 to 64 years receiving an intensive support intervention, and 30% higher in women aged 65 to 74 years receiving a motivation-support intervention, compared with nonobese/overweight individuals. The population attributable fractions in men and women aged 40 to 64 years receiving an intensive support intervention were 17.7% and 6.6%, respectively, while that in women aged 65 to 74 years receiving a motivation-support intervention was 9.4%. Compared with the supernormal group, nonobese/overweight individuals with risk factors had similar hazard ratios and population attributable fractions as individuals with metabolic syndrome.

CONCLUSIONS: Similar CVD excess and attributable risks among individuals with metabolic syndrome components in the absence and presence of obesity/overweight imply the need for lifestyle modification in both high-risk groups.

Key Words: cardiovascular disease ■ cohort study ■ incidence ■ metabolic syndrome ■ risk classification

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CLINICAL PERSPECTIVE

What Is New?

- In Japan, a diagnosis of metabolic syndrome (MetS) requires the presence of obesity/overweight in addition to other MetS components (high blood pressure, dyslipidemia, and high blood glucose), based on its pathophysiology.
- It is uncertain, however, whether the risk classification under the nationwide program on screening and lifestyle modification for MetS in Japan captures well high-risk individuals who could benefit from lifestyle modifications such as diet and alcohol modification, smoking cessation, and enhanced physical activity.
- This pooled analysis of 10 Japanese prospective cohort studies showed that nonobese/overweight individuals with other MetS components had similar excess and attributable risks of cardiovascular disease compared with individuals with MetS.

What Are the Clinical Implications?

- Because of the much lower prevalence of obesity/overweight in Japan compared with other high- and middle-income countries, a significant proportion of the population at high cardiovascular disease risk may be missed under the current program framework.
- The present findings may be useful for scientific communities and policymakers to construct cardiovascular disease preventive strategies and clinical practice guidelines not only in Japan but also other countries or populations where the prevalence of obesity is not largely common.

Nonstandard Abbreviations and Acronyms

CIRCS	Circulatory Risk in Communities Study
IHD	ischemic heart disease
ISI	intensive support intervention
ISO	information supply only
MetS	metabolic syndrome
MSI	motivation-support intervention
PAF	population attributable fraction
WHO	World Health Organization

Prevention of noncommunicable diseases is an urgent public health issue worldwide because over two thirds of deaths are caused by ischemic heart disease (IHD) and stroke.[1]

In 2008, the Japanese government conducted a nationwide program on screening and lifestyle interventions (modification of diets and alcohol consumption, smoking cessation, and enhanced physical activity) for the prevention and control of metabolic syndrome (MetS) to enhance the prevention of cardiovascular disease (CVD) and chronic kidney disease, and to attenuate the substantial and continuous increment of medical costs.[2]

MetS, a constellation of cardiovascular (metabolic) risk factors such as high blood pressure, dyslipidemia (low high-density lipoprotein [HDL] cholesterol and/or high triglyceride levels), and high blood glucose level, is expected to be prevented and controlled by the reduction of abdominal obesity.[3] Thus, the criteria for MetS in Japan constitute obesity/overweight as the essential component[4,5]; this is different from the criteria in Europe and the United States, which includes abdominal obesity as one of the components.[6] Additionally, the cut points of waist circumference at the umbilical level were 85 cm in men and 90 cm in women, corresponding to an area of abdominal adipose tissue ≥100 cm^2,[4,5] which were different from those of the Asian criteria (90 cm and 80 cm, respectively).[6] Since these factors increase the risk of CVD and chronic kidney disease, MetS is regarded as an efficient gateway for their prevention through lifestyle modification.[7]

Accordingly, the program focused on high-risk individuals with abdominal obesity/overweight, and nonobese/overweight individuals with other MetS components can be missed. There is less focus on the issue of nonobese/overweight individuals, and this may be a potential pitfall because Japan has a much lower prevalence of obesity/overweight[8,9] compared with other high- and middle-income countries.[10–12] Worldwide, there is a large variation in the prevalence of overweight and obesity among countries with different sociodemographic indices, although, in general, there is a rapid increase in prevalence and this has led to a global burden of disease including CVD.[12]

Previous population-based cohort studies in Japan showed that excess risk of CVD was found not only in obese/overweight individuals with cardiovascular (metabolic) risk factors but also in nonobese/overweight individuals with these risk factors.[13–19] However, these studies used the European, American, or World Health Organization (WHO) criteria for MetS, and none of them used the Japanese criteria to validate the risk classification.

This study used the data of 10 Japanese prospective cohort studies on over 30 000 middle-aged or elderly community-dwelling residents with their waist circumference values and risk factors, to examine the risk of incident CVD according to risk classification and explore the program's strengths and weaknesses.

Our a priori hypothesis was that excess and attributable risks of incident CVD, expressed in hazard ratios (HRs) and population attributable fractions (PAFs),

are similar among high-risk individuals with MetS components regardless of whether they are obese/overweight.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

The study participants included 31 843 (14 479 men and 17 364 women) community residents aged 40 to 74 years in 10 prospective cohort studies around Japan. The studies were composed of CIRCS (Circulatory Risk in Communities Study),[13,15] Funagata Study,[20] Hiroshima Community Study,[21] Hisayama Study,[22,23] Ozu Study,[15] Suita Study,[16] Tanno/Sobetsu Study,[24] Tomishiro Study,[25] and Toyama Employees Study[26] (alphabetical order). Through literature review and peer inquiry, we selected these cohort studies for our pooled analysis because they measured waist circumference and included the incidence of CVD (IHD and stroke) as part of their end points.

We excluded participants with histories of IHD or stroke, with missing values of waist circumference or risk factors (blood pressure, serum HDL cholesterol levels, serum triglyceride levels, or blood glucose levels) from the analyses, and the remaining 29 288 participants (13 257 men and 16 031 women) were used in the analyses.

The participants were followed to determine the incidence of CVD (IHD and stroke) and censored when they moved out of the communities or died.

Table S1 presents the sex-specific profile for each cohort, which includes the number of patients, the number of participants analyzed, response rate, baseline years, end of follow-up, median follow-up year, mean age, number of incident CVD, age-adjusted incidence rate of CVD, and smoking rate. The median follow-up period was 8.2 years in men and 9.1 years in women, and the patient-years was 109 289 and 145 868 patient-years for men and women, respectively.

The study was approved by the ethics committee of the University of Tokyo and Osaka University. Informed consent requirement was waived because of the use of anonymous secondary data for pooled analysis.

Baseline Examination

At the baseline survey, waist circumference was measured at the umbilical level at the timing of normal expiration using a tape measure. Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Systolic and diastolic blood pressures were measured by trained technicians using standard mercury sphygmomanometers on the right arm of seated participants after a 5-minute rest. Blood was drawn into a plain, siliconized glass tube, and the serum was separated. The proportion of patients fasting was 72%. Serum total cholesterol, HDL cholesterol, triglycerides, and serum glucose were measured using standardized methods. An interview was conducted to ascertain histories of CVD, smoking status, number of cigarettes smoked per day, and usual intake of alcohol in *go* units (a Japanese traditional unit of volume corresponding to 23 g ethanol).

The original Japanese criteria for MetS include high waist circumference of ≥85 cm in men and ≥90 cm in women but not high BMI ≥25 kg/m^2.[4] In this analysis, we adopted these criteria for risk classification according to the nationwide screening program to examine whether it can satisfactorily capture high-risk individuals who could benefit from lifestyle interventions.

The criteria for MetS were the presence of high waist circumference ≥85 cm in men and ≥90 cm in women and/or BMI ≥25.0 kg/m^2, an essential component plus 1 (probable MetS) or ≥2 (definite MetS) of the followings[7]: (1) systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg or medication use; (2) triglyceride level ≥1.69 mmol/L (150 mg/dL) and/or HDL cholesterol level <1.03 mmol/L (40 mg/d); and (3) fasting glucose level ≥5.55 mmol/L (100 mg/dL) or nonfasting glucose level ≥7.77 mmol/L (140 mg/dL) or medication use. The risk classification for lifestyle interventions was categorized into: (1) information supply only (ISO), (2) motivation-support intervention (MSI), and (3) intensive support intervention (ISI), based on sex, age (40–64 years and 65–74 years), current smoking status, and grade of MetS (probable or definite), as shown in Table 1. Current smoking was considered an additional risk factor when the number of the aforementioned risk factors was 1 for high waist circumference ≥85 cm in men and ≥90 cm in women, and when their number was 2 for waist circumference <85 cm in men and <90 cm in women and BMI ≥25.0 kg/m^2. When age was 65 to 75 years, the ISI collapsed into the MSI. The reference category for this program (legislated reference category) was nonobese/overweight individuals (waist circumference <85 cm in men and <90 cm in women and BMI <25.0 kg/m^2), regardless of risk factors.

The criteria for referral to local physicians for medical care were defined as: (1) hypertension: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or medication use; (2) dyslipidemia: triglyceride level ≥3.39 mmol/dL (300 mg/dL), and/or HDL cholesterol level <0.91 mmol/dL (35 mg/dL), and/or non–HDL cholesterol ≥4.40 mmol/L (170 mg/dL), or medication use; and (3) diabetes: fasting glucose level ≥7.0 mmol/dL (126 mg/dL) or nonfasting glucose level ≥11.1 mmol/dL (200 mg/dL) or medication use.

Table 1. Frame of Risk Classification in the Nationwide Program of Screening and Lifestyle Interventions for MetS

Nonobese/overweight	ISO	MSI	ISI
Waist <85 cm in men/<90 cm in women and BMI <25 kg/m², regardless of risk factors	Waist ≥85 cm in men/≥90 cm in women and 0 risk factor	Waist ≥85 cm in men/≥90 cm in women and 1 risk factor	Waist ≥85 cm in men/≥90 cm in women and ≥2 risk factors
	OR	OR	OR
	Waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m², and 0 risk factor	Waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m², and 1 or 2 risk factors	Waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m², and ≥3 risk factors

ISO indicates information supply only; MSI, motivation-support intervention; ISI, intensive support intervention; and MetS, metabolic syndrome. Components of risk factors are as follows: high blood pressure: systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or medication use; dyslipidemia: triglyceride level ≥1.69 mmol/L (150 mg/dL) and/or high-density lipoprotein cholesterol level <1.03 mmol/L (40 mg/dL); and high glucose: fasting glucose level ≥5.55 mmol/L (100 mg/dL) or nonfasting glucose level ≥7.77 mmol/L (140 mg/dL) or medication use. Current smoking is considered a risk factor when the number of the above risk factors=1 for waist ≥85 cm in men/≥90 cm in women, and their number=2 for waist <85 cm in men/<90 cm in women and body mass index (BMI) ≥25 kg/m². For ages 65 to 74 years, the ISI was collapsed into MSI.

End Point Determination

In this study, the end point was CVD (combined IHD and stroke) incidence. The ascertainment sources for CVD were an interview at annual cardiovascular risk survey, national insurance claims, ambulance records, and/or mailed questionnaires, and for fatal cases, death certificates were used to obtain data on the underlying causes of death (*International Classification of Diseases*, *Tenth Revision* [*ICD-10*], I20 to I25 and I46). To confirm the diagnosis, all living patients were telephoned or visited to obtain medical history, and their medical records were reviewed. For fatal cases, we also obtained histories from families and reviewed medical records.

The criteria for IHD were modified from those of the WHO Expert Committee.[27] IHD included definite or probable myocardial infarction, angina pectoris, and sudden cardiac death (death within 1 hour of onset, witnessed cardiac arrest, or abrupt collapse not preceded by ≥1 hours of symptoms). Stroke was defined as a focal neurological disorder with rapid onset, which persisted for at least 24 hours or until death.[27] The determination of incident strokes was conducted based on the clinical criteria and imaging study results available for ≥90% stroke events.[28] A panel of physician-epidemiologists, blinded to the data of risk factor surveys, made the final diagnoses for IHD and stroke.

Statistical Analysis

Person-years were calculated as the sum of individual follow-up time until the occurrence of incident CVD, death from other causes, emigration, or the end of 2008. To evaluate the validity of risk classification, we further divided the legislated reference category (nonobese/overweight regardless of risk factors) according to the number of risk factors into 3 subgroups: 0 risk factor (supernormal as new reference), 1 risk factor, and ≥2 risk factors, OR 0 risk factor (supernormal as new reference), no referral risk levels, and referral risk levels.

Subsequently, the sex- and age-specific HRs of CVDs and the respective 95% CIs were calculated with reference to the legislated category or supernormal group (nonobese/overweight individuals without risk factors), adjusting for age (years) and area (community), using the Cox proportional hazards model. To estimate the multivariable HRs, further adjustments were made to consider HDL cholesterol levels (mmol/L), ie, total serum cholesterol subtracted by HDL cholesterol, a major risk factor for CVD.[29] We did not adjust for smoking status and alcohol consumption because current smoking is one of the components for risk classification, and alcohol modification is one of the components for lifestyle interventions.

Regarding sensitivity analyses, the analyses of HRs were repeated when patients using medication for any of the risk factors were excluded because their lifestyle interventions had been trusted to attending physicians. Moreover, HRs were analyzed when the cutoff values of waist circumference were selected: 90 cm in men and 80 cm in women, regarded as the Asian criteria.[6]

We performed a competing risk analysis for death and moveout using Fine and Gray's subdistribution hazard model[30] and found these variables to have no significant effect on the HR estimates (<5% change). The assumption for proportionality was confirmed using an interaction term of the exposure and person-years of follow-up for all HR estimates (*P* values between 0.17 and 0.92).

We calculated the PAFs[31] and their 95% CIs[32] of CVD, which is the proportion of CVD events in the population that would be attributable to each category of MetS, with reference to the nonobese/overweight or supernormal group with the formula pd_i $(1–1/HR_i)$, where pd_i is the proportion among total cases, arising from the ith exposure category, and HR_i is the multivariable HR for the ith exposure category relative to the unexposed category.

Probability values for statistical tests were 2-tailed, and a $P<0.05$ was considered statistically significant. SAS statistical package (version 9.4, SAS Institute Inc) was used for all analyses.

RESULTS

Age- and sex-specific mean values±standard errors, and proportions of risk characteristics for the study participants are shown in Table S2. Then, we compared age- and sex-specific risk characteristics according to the legislated category of health instruction (Table S3). The proportions of those in the ISO, MSI, and ISI groups among participants aged 40 to 64 years were 5.6%, 10.2%, and 32.3% in men, and 6.7%, 13.6%, and 7.3% in women, respectively. The corresponding proportions of those in the ISO and MSI groups among participants aged 65 to 74 years were 3.4% and 41.5% in men, and 2.9% and 32.8% in women, respectively.

Expectedly, in both men and women aged 40 to 64 years and 65 to 74 years, mean levels and proportions of risk characteristics were progressively higher in the ISO, MSI, and ISI groups compared with those in the legislated reference group. Patients with hypertension were of the highest proportion, followed by those with dyslipidemia and diabetes, in each of the ISO, MSI, and ISI groups.

After the median 8.9 years of follow-up (255 156 patient-years), 535 patients (327 men and 208 women) aged 40 to 64 years at baseline were reported to have CVDs, as well were 488 patients (238 men and 250 women) aged 65 to 74 years at baseline. Table 2 shows sex-specific, age- and area-adjusted, and multivariable HRs for CVD, compared with the legislated reference group aged 40 to 64 years. The multivariable HRs of CVD were 0.64 (95% CI, 0.31–1.31) for the ISO group, 0.94 (95% CI, 0.61–1.44) for the MSI group, and 1.60 (95% CI, 1.26–2.04) for the ISI group, respectively, in men, and 0.25 (95% CI, 0.08–0.77), 0.98 (95% CI, 0.66–1.46), and 1.71 (95% CI, 1.16–2.54), respectively, in women, indicating no excess risk of CVD for the ISO and MSI groups, which was present for the ISI group in both sexes. The corresponding HRs among patients aged 65 to 74 years were 0.75 (95% CI, 0.33–1.71) and 1.23 (95% CI, 0.95–1.61) in men, and 0.55 (95% CI, 0.17–1.72) and 1.31 (95% CI, 1.01–1.69) in women, indicating no excess risk of CVD for the ISO group in both sexes, which was present for the MSI group in women. The PAFs of CVD for the ISI group versus the reference category of patients aged 40 to 64 years was 17.7% (95% CI, 8.2–26.2) in men and 6.6% (95% CI, 0.8–12.1) in women. The PAFs of CVD for the MSI group versus the reference category of patients aged 65 to 74 years was 9.4% (95% CI, 0.3–18.1) in women.

Subsequently, we analyzed the data with reference to the supernormal group (nonobese/overweight and 0 risk factor). The baseline characteristics were examined according to a new subgrouping of: (1) nonobese/overweight with 1 risk factor, and (2) nonobese/overweight with ≥2 risk factors, compared with the supernormal group (Table S4). As expected, among both men and women aged 40 to 64 years and 65 to 74 years, mean levels and proportions of risk characteristics were progressively higher in the nonobese/overweight subgroups with 1 risk factor and those with ≥2 risk factors.

Table 3 and the Figure indicate sex-specific, age- and area-adjusted, and multivariable HRs of CVD for the 2 nonobese/overweight subgroups and the ISO, MSI, and ISI groups, compared with the supernormal group, among patients aged 40 to 64 years and 65 to 74 years. Among patients aged 40 to 64 years, there were excess risks of CVD for the nonobese/overweight subgroup with ≥2 risk factors, for the MSI and ISI groups in both sexes, and even for the nonobese/overweight subgroup with 1 risk factor in women. The corresponding multivariable HRs were 2.41 (95% CI, 1.51–3.84), 1.71 (95% CI, 0.96–3.05), and 2.95 (95% CI, 1.86–4.68) in men, and 3.23 (95% CI, 1.98–5.28), 2.23 (95% CI, 1.31–3.80), and 4.03 (95% CI, 2.36–6.89) in women, and even 2.89 (95% CI, 1.83–4.55) in women. The PAFs of CVD for the nonobese/overweight subgroup with ≥2 risk factors were 17.9% (95% CI, 9.7–25.4) in men and 15.9% (95% CI, 8.9–22.5) in women, and that for the nonobese/overweight subgroup with 1 risk factor was 21.1% (95% CI, 12.2–29.0) in women, which was smaller than that for the ISI group in men

and even larger than those for the MSI and ISO groups in women.

Among patients aged 65 to 74 years, significant excess risks of CVD were found for the nonobese/overweight subgroup with ≥2 risk factors and the MSI group. The corresponding multivariable HRs were 2.05 (95% CI, 1.18–3.57) and 2.17 (95% CI, 1.25–3.76) in men, and 2.71 (95% CI, 1.57–4.68) and 2.45 (95% CI, 1.44–4.18) in women. The PAFs of CVD for the nonobese/overweight subgroup with ≥2 risk factors were 17.7% (95% CI, 5.7–28.1) in men, and 19.4% (95% CI, 10.4–27.6) in women, which were slightly lower than those for the MSI group.

We recategorized the abovementioned nonobese/overweight subgroups with risk factors according to the absence or presence of a referral to local physicians, ie, the nonobese/overweight subgroups that did not need a referral and those that needed a referral. The baseline characteristics are shown according to nonobese/overweight subgroups with or without the need for a referral, and according to ISO, MSI (without or with referral), and ISI (without or with referral) groups compared with the supernormal group (Table S5). As expected, even within the new subgroups, there was a gradient in the mean levels and proportions of risk characteristics.

Table 4 indicates sex-specific and age- and area-adjusted HRs (95% CIs) of CVD for these 2 nonobese/overweight subgroups, and for the ISO, MSI (without or with referral), and ISI (without or with referral) groups compared with the supernormal group among patients aged 40 to 64 years and 65 to 74 years. There were significant excess risks of CVD for the nonobese/overweight subgroup that needed referral in both men and women and even in the nonobese/overweight subgroup that did not need a referral in women. Among patients aged 40 to 64 years, the multivariable HRs of CVD for the nonobese/overweight subgroup that needed a referral were 2.97 (95% CI, 1.86–4.75) in men and 3.75 (95% CI, 2.39–5.89) in women, and that for the nonobese/overweight subgroup that did not need a referral in women was 1.99 (95% CI, 1.16–3.31); the corresponding PAFs were 20.9% (95% CI, 13.3–27.8) in men and 31.0% (95% CI, 21.4–39.4) and 6.5% (95% CI, 0.9–11.7) in women. In men, the multivariable HR of CVD for the nonobese/overweight subgroup that needed a referral was similar to that for the MSI that needed a referral, but the PAF was much larger for the nonobese/overweight subgroup than for the MSI group. In women, the multivariable HR of CVD for the nonobese/overweight subgroup that needed a referral was between that for the ISI and the MSI groups that needed a referral, but the PAF was much larger for the nonobese/overweight subgroup than for the ISI and MSI groups.

Among patients aged 65 to 74 years, the significant excess risk of CVD was found for the nonobese/overweight subgroup that needed a referral, and the multivariable HRs of CVD were 2.21 (95% CI, 1.28–3.84) in men and 2.18 (95% CI, 1.29–3.70) in women. The corresponding PAFs were 20.3% (95% CI, 8.3–30.8) and 23.0% (95% CI, 10.0–35.9), respectively. In men, the multivariable HR and PAF of CVD for the nonobese/overweight subgroup that needed a referral were similar to the HR and PAF for the MSI group that needed a referral. In women, the multivariable HR of CVD for the nonobese/overweight subgroup that needed a referral was similar to the HR for the MSI group that did not need or did need a referral. However, the PAF was larger for the nonobese/overweight subgroup than for both MSI groups.

The HRs and PAFs did not differ materially among all groups when we excluded patients who used medication for hypertension, diabetes, or dyslipidemia (Tables S6 and S7). The significance and magnitude of HRs did not substantially change when the cutoff points of waist circumference were selected, 90 cm in men and 80 cm in women, as per the international Asian criteria. Because the proportion of the ISI group became smaller in men aged 40 to 64 years, that of the MSI group became smaller in men aged 65 to 74 years, and those of the MSI and ISI groups became larger in women; the corresponding PAFs varied accordingly (Tables S8 and S9).

DISCUSSION

In the present pooled analyses of 10 population-based prospective cohort studies of men and women aged 40 to 74 years, the risk of CVD was ≈60% to 70% higher in the legislated group of ISI among men and women aged 40 to 64 years, and ≈30% higher for the legislated group of MSI among women aged 65 to 74 years, compared with the nonobese/overweight reference group. A significant PAF of 18% was found in the ISI group among men aged 40 to 64 years but not among women aged 40 to 64 years and men and women aged 65 to 74 years. The MSI groups in men and women aged 40 to 64 years and men aged 65 to 74 years did not show excess risks of CVD because the reference group included high-risk individuals (nonobese/overweight but with ≥1 risk factors). The impact of MetS as an attributable risk for CVD was larger in middle- than in older-aged individuals. Among middle-aged individuals, it was larger in men than in women.

When we made the supernormal group (nonobese/overweight and no risk factor) a reference, 2 to 4 times higher risk of CVD was observed in not only the MSI and ISI groups but also in the nonobese/overweight subgroup with ≥2 risk factors in

Table 2. Age- and Sex-Specific HRs of CVD According to the Legislated Category of Health Intervention for Screened Participants

	Nonobese/overweight (reference)	Obese/overweight: lifestyle intervention		
		ISO	MSI	ISI
		Waist ≥85 cm in men/≥90 cm in women and 0 risk factor OR	Waist ≥85 cm in men/≥90 cm in women and 1 risk factor OR	Waist ≥85 cm in men/≥90 cm in women and ≥2 risk factors OR
	Waist <85 cm in men/<90 cm in women and BMI <25 kg/m^2, regardless of risk factors	waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and 0 risk factor	waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and 1 or 2 risk factors	waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and ≥3 risk factors
Age, 40–64 y				
Men, n	5443	588	1075	3389
No. of patient-y	47 809	5003	8578	25 999
No. of cases	140	8	25	154
Age- and area-adjusted HR (95% CI)	1.00	0.65 (0.32–1.33)	0.97 (0.63–1.48)	1.70 (1.34–2.14)
Multivariable HR (95% CI)	1.00	0.64 (0.31–1.31)	0.94 (0.61–1.44)	1.60 (1.26–2.04)
PAF (95% CI)		…	…	17.7 (8.2–26.2)
Women, n	8776	806	1643	882
No. of patient-y	80 776	7867	15 784	7831
No. of cases	142	3	30	33
Age- and area-adjusted HR (95% CI)	1.00	0.25 (0.08–0.77)	0.96 (0.65–1.43)	1.66 (1.13–2.46)
Multivariable HR (95% CI)	1.00	0.25 (0.08–0.77)	0.98 (0.66–1.46)	1.71 (1.16–2.54)
PAF (95% CI)		–	–	6.6 (0.8–12.1)
Age, 65–74 y				
Men, n	1521	95	1146	
No. of patient-y	12 582	785	8534	
No. of cases	127	6	105	
Age- and area-adjusted HR (95% CI)	1.00	0.75 (0.33–1.71)	1.23 (0.95–1.60)	
Multivariable HR (95% CI)	1.00	0.75 (0.33–1.71)	1.23 (0.95–1.61)	
PAF (95% CI)		–	–	
Women, n	2523	115	1286	
No. of patient-y	21 707	981	10 922	
No. of cases	148	3	99	
Age- and area-adjusted HR (95% CI)	1.00	0.55 (0.17–1.72)	1.31 (1.02–1.70)	
Multivariable HR (95% CI)	1.00	0.55 (0.17–1.72)	1.31 (1.01–1.69)	
PAF (95% CI)		…	9.4 (0.3–18.1)	

BMI indicates body mass index; CVD, cardiovascular disease; ISI, intensive support intevention; ISO, information supply only; MSI, motivation-support intervention; and PAF, population attributable fraction. Multivariable hazard ratio (HR): adjusted further for non–high-density lipoprotein (HDL) cholesterol. For ages 65 to 74 years, the ISI was collapsed into MSI.

Table 3. Age- and Sex-Specific HRs of Total CVD According to the Refined Category of Health Intervention With Nonobese/Overweight Subtypes for Screened Participants

	Nonobese/overweight			Obese/overweight: lifestyle intervention		
	Supernormal (reference)	Nonobese/overweight and 1 risk factor	Nonobese/overweight and ≥2 risk factors	ISO	MSI	ISI
	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and 0 risk factor	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and 1 risk factor	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and ≥2 risk factors	Waist ≥85 cm in men/≥90 cm in women and 0 risk factor OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and 0 risk factor	Waist ≥85 cm in men/≥90 cm in women and 1 risk factor OR waist <85 cm in men/<90 cm in women and BMI ≥25 kg/m^2, and 1 or 2 risk factors	Waist ≥85 cm in men/≥90 cm in women and ≥2 risk factors OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and ≥3 risk factors
Age, 40–64 y						
Men, n	1747	1008	2688	588	1075	3389
No. of patient-y	16 243	8409	23 157	5003	8578	25 999
No. of cases	22	18	100	8	25	154
Age- and area-adjusted	1.00	1.30 (0.69–2.42)	2.48 (1.56–3.95)	1.18 (0.53–2.66)	1.79 (1.00–3.17)	3.14 (2.00–4.95)
Multivariable HR (95% CI)	1.00	1.27 (0.68–2.38)	2.41 (1.51–3.84)	1.15 (0.51–2.58)	1.71 (0.96–3.05)	2.95 (1.86–4.68)
PAF (95% CI)		…	17.9 (9.7–25.4)	…	…	31.1 (20.9–40.1)
Women, n	4372	2842	1562	806	1643	882
No. of patient-y	39 865	26 583	14 328	7867	15 784	7831
No. of cases	27	67	48	3	30	33
Age- and area-adjusted	1.00	2.82 (1.79–4.44)	3.05 (1.88–4.95)	0.52 (0.16–1.70)	2.09 (1.24–3.55)	3.70 (2.19–6.26)
Multivariable HR (95% CI)	1.00	2.89 (1.83–4.55)	3.23 (1.98–5.28)	0.53 (0.16–1.75)	2.23 (1.31–3.80)	4.03 (2.36–6.89)
PAF (95% CI)		21.1 (12.2–29.0)	15.9 (8.9–22.5)	…	7.9 (2.1–13.4)	10.8 (5.5–15.8)
Age, 65–74 y						
Men, n	301	372	848	95	1146	
No. of patient-y	2574	3104	6904	785	8534	
No. of cases	15	30	82	6	105	
Age- and area-adjusted	1.00	1.69 (0.91–3.14)	2.04 (1.18–3.55)	1.31 (0.51–3.38)	2.15 (1.25–3.70)	
Multivariable HR (95% CI)	1.00	1.70 (0.91–3.16)	2.05 (1.18–3.57)	1.32 (0.51–3.40)	2.17 (1.25–3.76)	
PAF (95% CI)		…	17.7 (5.7–28.1)	…	23.8 (9.5–35.8)	

(*Continued*)

Table 3. Continued

	Nonobese/overweight			Obese/overweight: lifestyle intervention		
	Supernormal (reference)	Nonobese/overweight and 1 risk factor	Nonobese/overweight and ≥2 risk factors	ISO	MSI	ISI
	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and 0 risk factor	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and 1 risk factor	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and ≥2 risk factors	Waist ≥85 cm in men/≥90 cm in women and 0 risk factor OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and 0 risk factor	Waist ≥85 cm in men/≥90 cm in women and 1 risk factor OR waist <85 cm in men/<90 cm in women and BMI ≥25 kg/m^2, and 1 or 2 risk factors	Waist ≥85 cm in men/≥90 cm in women and ≥2 risk factors OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and ≥3 risk factors
Women, n	566	1130	827	115	1286	
No. of patient-y	4744	9949	7013	981	10 922	
No. of cases	16	55	77	3	99	
Age- and area-adjusted	1.00	1.55 (0.89–2.70)	2.67 (1.55–4.59)	0.99 (0.29–3.41)	2.41 (1.42–4.10)	
Multivariable HR (95% CI)	1.00	1.55 (0.89–2.71)	2.71 (1.57–4.68)	0.99 (0.29–3.41)	2.45 (1.44–4.18)	
PAF (95% CI)		…	19.4 (10.4–27.6)	…	23.4 (11.8–33.5)	

BMI indicates body mass index; CVD, cardiovascular disease; ISI, intensive support intervention; ISO, information supply only; MSI, motivation-support intervention; and PAF, population attributable fraction. Multivariable hazard ratio (HR): adjusted further for non–high-density lipoprotein (HDL) cholesterol. For ages 65 to 74 years, the ISI was collapsed into MSI.

Table 4. Age- and Sex-Specific HRs of Total CVD According to the Refined Category of Health Intervention With Nonobese/Overweight and Referral Subtypes for Screened Participants

	Nonobese/nonoverweight			Obese/overweight: lifestyle intervention				
	Super normal (reference)	Nonobese/ overweight and no need for referral	Nonobese/ overweight and need for referral	ISO	MSI		ISI	
	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and 0 risk factor	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and no referral risk levels	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and referral risk levels	Waist ≥85 cm in men/ ≥90 cm in women and 0 risk factor OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and 0 risk factor	Waist ≥85 cm in men/≥90 cm in women and 1 risk factor OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, 1 or 2 risk factors,		Waist ≥85 cm in men/≥90 cm in women and ≥2 risk factors OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and ≥3 risk factors,	
					Plus no referral risk levels	Plus referral risk levels	Plus no referral risk levels	Plus referral risk levels
Age, 40–64 y								
Men, n	1747	1519	2177	588	445	630	745	2644
No. of patient-y	16 243	13 392	18 173	5003	3914	4664	6111	19 888
No. of cases	22	15	103	8	4	21	15	139
Age and area-adjusted HR (95% CI)	1.00	0.76 (0.40–1.47)	3.04 (1.91–4.83)	1.18 (0.53–2.65)	0.67 (0.23–1.94)	2.64 (1.44–4.82)	1.47 (0.76–2.85)	3.78 (2.40–5.97)
Multivariable HR (95% CI)	1.00	0.76 (0.40–1.47)	2.97 (1.86–4.75)	1.16 (0.52–2.62)	0.67 (0.23–1.95)	2.64 (1.44–4.85)	1.47 (0.76–2.86)	3.79 (2.38–6.05)
PAF (95% CI)		…	20.9 (13.3–27.8)	…	…	4.0 (1.0–6.9)	…	31.3 (22.9–38.8)
Women, n	4372	1806	2598	806	579	1064	149	733
No. of patient-y	39 865	17 853	23 057	7867	5995	9790	1534	6297
No. of cases	27	27	88	3	7	23	4	29
Age- and area-adjusted	1.00	2.00 (1.17–3.43)	3.44 (2.20–5.37)	0.52 (0.16–1.70)	1.73 (0.75–3.99)	2.33 (1.33–4.11)	3.11 (1.08–8.96)	3.98 (2.32–6.84)
Multivariable HR (95% CI)	1.00	1.99 (1.16–3.31)	3.75 (2.39–5.89)	0.54 (0.16–1.77)	1.78 (0.77–4.10)	2.63 (1.48–4.67)	3.25 (1.13–9.37)	4.60 (2.64–8.01)
PAF (95% CI)		6.5 (0.9–11.7)	31.0 (21.4–39.4)	…	…	6.9 (2.0–11.5)	1.3 (0.0–3.2)	10.9 (5.8–15.8)
Age, 65–74 y								
Men, n	301	385	835	95	224	922		
No. of patient-y	2574	3332	6674	785	1764	6770		
No. of cases	15	24	88	6	11	94		

(*Continued*)

Table 4. Continued

	Nonobese/nonoverweight			Obese/overweight: lifestyle intervention				
	Super normal (reference)	Nonobese/ overweight and no need for referral	Nonobese/ overweight and need for referral	ISO	MSI		ISI	
	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and 0 risk factor	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and no referral risk levels	Waist <85 cm in men/<90 cm in women, BMI <25 kg/m^2, and referral risk levels	Waist ≥85 cm in men/ ≥90 cm in women and 0 risk factor OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and 0 risk factor	Waist ≥85 cm in men/≥90 cm in women and 1 risk factor OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, 1 or 2 risk factors,		Waist ≥85 cm in men/≥90 cm in women and ≥2 risk factors OR waist <85 cm in men/<90 cm in women, BMI ≥25 kg/m^2, and ≥3 risk factors,	
					Plus no referral risk levels	Plus referral risk levels	Plus no referral risk levels	Plus referral risk levels
Age and area-adjusted HR (95% CI)	1.00	1.36 (0.71–2.59)	2.19 (1.26–3.79)	1.31 (0.51–3.37)	1.17 (0.54–2.55)	2.46 (1.43–4.26)		
Multivariable HR (95% CI)	1.00	1.36 (0.71–2.60)	2.21 (1.28–3.84)	1.31 (0.51–3.40)	1.19 (0.54–2.60)	2.53 (1.46–4.40)		
PAF (95% CI)		…	20.3 (8.3–30.8)	…	…	23.9 (12.2–34.0)		
Women, n	566	534	1423	115	231	1055		
No. of patient-y	4744	4810	12 152	981	2029	8893		
No. of cases	16	27	105	3	14	85		
Age- and area-adjusted HR (95% CI)	1.00	1.69 (0.91–3.13)	2.17 (1.28–3.68)	0.99 (0.29–3.42)	2.07 (1.01–4.24)	2.69 (1.58–4.60)		
Multivariable HR (95% CI)	1.00	1.69 (0.91–3.13)	2.18 (1.29–3.70)	0.99 (0.29–3.42)	2.08 (1.01–4.26)	2.71 (1.58–4.65)		
PAF (95% CI)		…	23.0 (10.0–35.9)	…	2.9 (0.0–6.1)	21.4 (11.7–30.1)		

BMI indicates body mass index; CVD, cardiovascular disease; ISI, intensive support intervention; ISO, information supply only; MSI, motivation-support intervention; and PAF, population attributable fraction. Referral risk levels were defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or medication use; triglycerides level ≥3.39 mmol/L (300 mg/dL) and/or high-density lipoprotein (HDL) cholesterol level ≤0.91 mmol/L (34 mg/dL) or non–HDL cholesterol level ≥4.40 mmol/L (170 mg/dL) or medication use; and fasting glucose level ≥7.0 mmol/L (126 mg/dL) or nonfasting glucose level ≥1.11 mmol/L (200 mg/dL) or medication use. Multivariable hazard ratio (HR): adjusted further for non–high-density lipoprotein (HDL) cholesterol. For ages 65 to 74 years, the ISI was collapsed into MSI.

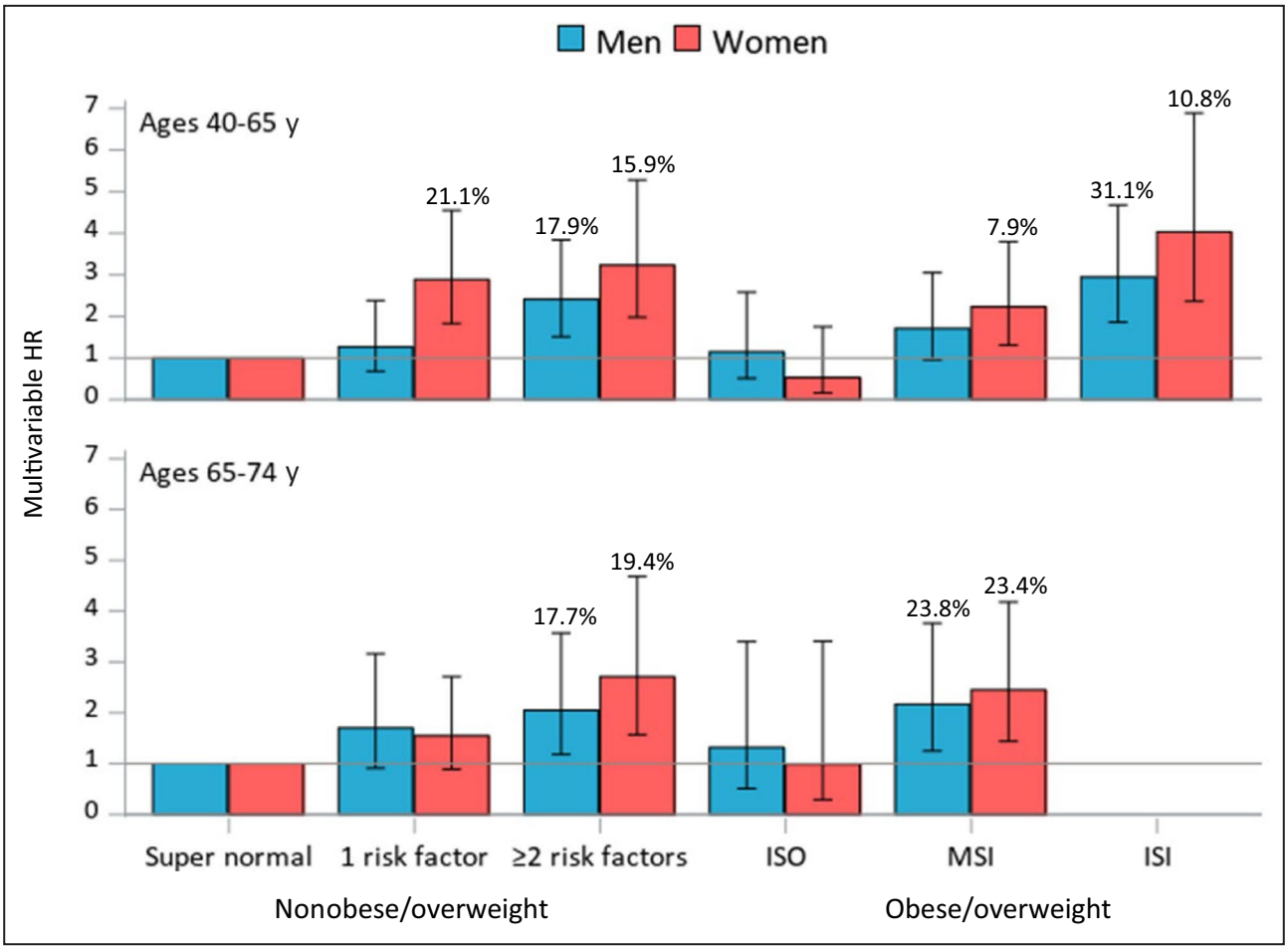

Figure. Age- and sex-specific multivariable hazard ratios (HRs) of cardiovascular diseases for nonobese/overweight subgroups with risk factors and information supply only (ISO), motivation-support intervention (MSI), and intensive support intervention (ISI) groups, compared with the supernormal group.
Bar: 95% CI. The number of percentages: population attributable risk.

men and women aged 40 to 64 years, and in the nonobese/overweight subgroup with 1 risk factor in women aged 40 to 64 years. The PAF for the nonobese/overweight subgroup with ≥2 risk factors was smaller in men but larger in women, compared with that for the ISI group.

In women, the PAF was similar in the nonobese/overweight subgroup with 1 risk factor compared with that in the MSI group. Another subgrouping of nonobese/overweight individuals with either no need or a need for referral showed similar results. These findings did not materially alter when we excluded patients using medication for risk factors, and when we used the Asian criteria of waist circumference cut points. Therefore, nonobese/overweight individuals with risk factors had an elevated risk of CVD as did individuals with MetS. Thus, the impact of the nonobese/overweight subgroup with risk factors was similar to that of groups with MetS. This study implies that a significant proportion of high-risk individuals, who could have benefitted from lifestyle modification, may be missed under the current program framework.

Previous prospective studies of middle-aged Japanese men and women have consistently indicated that MetS is associated with an increased incidence of and mortality from IHD, stroke, and CVD.[13–19,22–24] However, these studies used European, American or WHO criteria, which include abdominal obesity as one of the components but not as an essential component as in the Japanese criteria. Again, this study is the first to examine the validity of the risk classification under the national screening for MetS based on Japanese criteria.

A unique characteristic of the components of MetS in Japanese populations is the low average BMI and the low prevalence of obesity compared with those in the United States and other countries. According to national surveys in Japan and the United States, mean BMI levels among adults have remained low (22–23 kg/m^2) with a slight increase in men (still <24 kg/m^2) and

a slight decline in women in Japan between the 1970s and the 2010s,[8,9]while there was a sharp increase in the United States from 25 kg/m^2 to 30 kg/m^2 between 1999 to 2000 and 2015 to 2016.[10,11] The prevalence of overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) were ≈20% to 30% and 3% to 5%, respectively, in Japanese patients,[8,9] but 70% to 80% and 20% to 30% in American patients[10,11] in the 2010s. Because of such a low prevalence of obesity in Japan, we need to screen patients with MetS (with abdominal obesity or overweight as an essential component) as high-risk individuals and as high-risk individuals without abdominal obesity or overweight who may need lifestyle modification for the prevention of CVD. On the other hand, in countries with a high prevalence of obesity/overweight such as in the United States, there may be less focus on the screening of nonobese/overweight individuals as being at high risk.

In this study, we found an excess risk of CVD within the subgroups of the legislated reference group because they included nonobese/overweight individuals with other MetS components of the risk factors. Among them, the most common risk factors were high blood pressure, followed by dyslipidemia and high glucose levels. High salt intake and high alcohol consumption have been regarded as major determinants of hypertension among nonoverweight individuals.[33] Diabetes in nonoverweight individuals is commonly observed in Japanese individuals, probably because of the lower reserve for insulin secretion compared with that in White individuals.[34,35]

A recent systematic review indicated that behavioral counseling to promote a healthy diet and physical activity was effective in improving diet and increasing physical activity for adults with cardiovascular risk factors. It is also effective in reducing cardiovascular risk factors and cardiovascular events.[36] In both younger-/middle- and older-aged groups, the effect of lifestyle intervention on the reduction of systolic blood pressure, blood total cholesterol, and weight was evident. Further, overweight/obese and nonoverweight/obese individuals illustrated the effects of lifestyle intervention on the reduction of blood total cholesterol.[36] Our previous randomized controlled trials demonstrated that lifestyle modification reduced cardiovascular risk factors such as systolic blood pressure[37,38] and blood total cholesterol[39] among Japanese men and women with a mean BMI of 24 to 25 kg/m^2. However, there has been no empirical evidence of whether the intervention effect varies with sex.[36]

The strengths of this study include a large population-based sample of men and women and the use of standardized methods for the measurement of waist circumference and other risk characteristics. Additionally, the methods of surveillance for CVD, including myocardial infarction, angina pectoris, sudden cardiac death, and stroke, were similar among the 10 cohorts.

The study limitations are as follows. First, there were a small number of CVD cases in the ISO group, so we did not find any significant HRs. Second, 28% of the study patients were not fasting, so we used a nonfasting serum triglyceride level ≥1.69 mmol/L (150 mg/dL) as a component of MetS. Although the use of the same cutoff point as fasting status has been controversial, data on nonfasting triglycerides can be used because they are a significant or even stronger predictor for IHD and stroke among Japanese individuals.[40]

CONCLUSIONS

The present study supports that the system for screening for patients with MetS to conduct lifestyle interventions and, if needed, referral to local physicians is justified in terms of risk stratification for CVD. Our study also implies the need for lifestyle modification for middle-aged nonobese/overweight men and women with ≥2 risk factors and even middle-aged nonobese/overweight women with only 1 risk factor or no referral risk levels because they had 2 to 4 times excess risk of CVD, compared with the supernormal group (nonobese/overweight and no risk factor). Because of the lower prevalence of obesity/overweight in Japan compared with middle- or high-income countries, a significant proportion of the population at high CVD risk may be missed under the current framework of the program.

The present findings may be useful for scientific communities and policymakers to construct CVD preventive strategies and clinical practice guidelines in Japan as well as in other countries or populations where the prevalence of obesity is not common.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S9

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SUPPLEMENTAL MATERIAL

Table S1. Population Profiles in Men and Women Aged 40-74 Years.

	No. of subjects	No. at participants analyzed	Response rate, %	Baseline year	End of follow-up	Median of follow-up year	Person-year	Mean age, y	No. of CVD cases	Age-adjusted CVD incidence per 1,000 person-year	Smoking rate, %
Men											
CIRCS	2808	1701	61	1988-1993	2005	13.4	22784	56.7	80	5.4	50.9
Funagata study	692	426	62	1990-1993	2002	8.2	3511	54.3	17	5.1	61.1
Hiroshima Community Study	1152	764	66	1996-1997	2003	5.5	4203	61.2	36	5.2	48.6
Hisayama Study	1691	972	57	1998	2012	12.4	12017	55.0	101	3.7	50.6
Ozu Study	3466	1341	39	1996-1998	2008	9.9	13338	62.0	67	7.7	38.1
Suita Study	4270	2108	49	1989-1993	2002	5.9	12515	57.7	87	6.0	50.3
Tanno/Sobetsu Study	2149	633	29	1994	2008	11.1	7028	60.6	73	6.8	53.6
Tomishiro Study	8386	3076	37	2003-2004	2008	3.7	11227	51.9	56	2.7	31.3
Toyama Employees Study	2423	2236	92	1996	2012	10.1	22664	48.5	48	2.7	57.6
Subtotal	27037	13257	49			8.2	109289	56.4	565	4.8	46.8
Women											
CIRCS	4644	2994	64	1988-1993	2005	13.6	40836	56.6	87	2.8	6.3
Funagata study	749	522	70	1990-1993	2002	8.6	4471	55.0	9	3.4	3.7
Hiroshima Community Study	2289	1447	63	1996-1997	2003	5.7	8207	64.3	50	3.5	9.9
Hisayama Study	1887	1272	67	1998	2012	13.1	16702	55.6	94	2.8	6.6

Ozu Study	4112	2576	63	1996-1998	2008	10.5	27032	60.1	59	4.2	3.0
Suita Study	4720	2404	51	1989-1993	2002	6.1	14664	56.6	47	3.2	11.2
Tanno/Sobetsu Study	2203	936	42	1994	2008	11.6	10854	59.4	71	3.7	8.2
Tomishiro Study	8391	2635	31	2003-2004	2008	3.7	9762	52.2	26	2.0	4.0
Toyama Employees Study	1334	1245	93	1996	2012	10.7	13341	48.2	15	4.0	1.9
Subtotal	30329	16031	53			9.1	145868	56.4	458	3.3	6.2

Table S2. Age- and Sex-specific Risk Characteristics According to the Legislated Category of Health Intervention for Screened Participants.

	Men	Women
Age, 40-64 y		
No. of participants	10,495	12,107
Age, y	51.5±6.9	52.5±7.0
Current smokers, %	48.9	6.4
Waist circumference, cm	83.5±8.2	79.0±9.8
Body mass index, kg/m^2	23.8±3.0	23.2±3.2
Systolic blood pressure, mmHg	128.1±17.2	123.7±18.2
Diastolic blood pressure, mmHg	80.4±11.2	75.5±11.0
Medication use for hypertension, %	12.3	11.8
Triglycerides, mmol/L	1.70±1.28	1.25±0.81
HDL-cholesterol, mmol/L	1.35±0.36	1.53±0.37
Total cholesterol, mmol/L	5.22±0.90	5.44±0.95
Non-HDL-cholesterol, mmol/L	3.86±0.93	3.91±0.98
Medication use for dyslipidemia, %	2.9	3.3
Fasting blood glucose, mmol/L	5.65±1.24	5.33±0.94
Non-fasting blood glucose, mmol/L	6.62±2.27	6.03±1.71
Medication use for diabetes, %	16.8	12.7
Hypertensives, %	51.5	40.0
Dyslipidemia, %	41.8	21.4
Diabetes, %	7.6	3.6

Age, 65-74 y		
No. of participants	2,762	3,924
Age, y	68.8±2.8	69.0±2.8
Current smokers, %	38.8	5.6
Waist circumference, cm	82.8±8.7	82.1±10.2
Body mass index, kg/m^2	22.8±3.0	23.4±3.4
Systolic blood pressure, mmHg	136.1±19.2	136.4±19.8
Diastolic blood pressure, mmHg	79.2±11.0	77.5±10.8
Medication use for hypertension, %	24.3	27.7
Triglycerides, mmol/L	1.50±0.94	1.49±0.86
HDL-cholesterol, mmol/L	1.36±0.38	1.47±0.37
Total cholesterol, mmol/L	5.03±0.90	5.64±0.93
Non-HDL-cholesterol, mmol/L	3.67±0.92	4.18±0.95
Medication use for dyslipidemia, %	3.5	7.2
Fasting blood glucose, mmol/L	5.77±1.40	5.52±1.00
Non-fasting blood glucose, mmol/L	6.68±2.30	6.22±1.91
Medication use for diabetes, %	5.5	3.9
Hypertensives, %	69.3	69.5
Dyslipidemia, %	36.7	31.4
Diabetes, %	10.2	6.2

Table S3. Age- and Sex-specific Risk Characteristics According to the Legislated Category of Health Intervention for Screened Participants.

		Obese/overweight: lifestyle intervention		
	Non-obese/overweight (reference)	ISO	MSI	ISI
	Waist <85cm men/<90cm in women and BMI <25kg/m^2, regardless of risk factors	Waist ≥85cm in men/≥90cm in women and 0 risk factor OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥85cm in men/≥90cm in women and 1 risk factor OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors	Waist ≥85cm in men/ ≥90cm in women and ≥2 risk factors OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and ≥3 risk factors
Age, 40-64 y				
Men				
No. of participants	5,443	588	1,075	3,389
Age, y	51.3±7.0	49.9±6.7	51.7±6.8	52.2±6.9
Current smokers, %	53.4	46.7	6.7	55.2
Waist circumference, cm	77.4±5.0	87.8±4.3	87.8±5.4	90.9±5.5
Body mass index, kg/m^2	21.8±1.8	25.3±1.9	25.8±2.0	26.1±2.5
Systolic blood pressure, mmHg	124.7±16.7	115.9±8.3	128.6±16.1	135.5±16.5
Diastolic blood pressure, mmHg	77.8±10.9	73.8±6.7	81.9±10.2	85.2±10.7
Medication use for hypertension, %	7.8	0	12.7	21.7
Triglycerides, mmol/L	1.43±1.11	1.12±0.31	1.55±0.98	2.29±1.50
HDL-cholesterol, mmol/L	1.44±0.39	1.38±0.26	1.34±0.32	1.21±0.30
Total cholesterol, mmol/L	5.11±0.90	5.17±0.81	5.28±0.82	5.38±0.91
Non-HDL-cholesterol, mmol/L	3.67±0.92	3.79±0.80	3.94±0.84	4.16±0.91
Medication use for dyslipidemia, %	1.9	1.7	2.7	4.8

Fasting blood glucose, mmol/L	5.48±1.17	5.06±0.33	5.48±0.87	6.07±1.43
Non-fasting blood glucose, mmol/L	6.44±2.18	5.82±0.87	6.08±1.07	7.25±2.71
Medication use for diabetes, %	2.3	0	1.3	4.9
Hypertensives, %	42.1	0	50.6	75.9
Dyslipidemia, %	30.1	0	31.6	71.0
Diabetes, %	5.6	0	3.6	13.5
Women				
No. of participants	8,776	806	1,643	882
Age, y	52.0±7.0	51.4±6.9	53.8±6.7	55.5±6.2
Current smokers, %	6.5	5.9	2.0	13.5
Waist circumference, cm	75.2±7.2	86.8±8.0	87.6±7.4	94.5±6.6
Body mass index, kg/m^2	21.7±2.0	26.4±1.9	27.0±2.2	27.8±3.0
Systolic blood pressure, mmHg	121.2±17.6	114.9±9.0	133.0±17.7	139.9±16.2
Diastolic blood pressure, mmHg	73.9±10.6	71.7±7.27	81.1±10.9	84.1±10.2
Medication use for hypertension, %	8.7	0	21.7	35.9
Triglycerides, mmol/L	1.15±0.73	1.01±0.33	1.48±0.88	2.05±1.15
HDL-cholesterol, mmol/L	1.58±0.37	1.53±0.31	1.43±0.33	1.28±0.30
Total cholesterol, mmol/L	5.37±0.93	5.38±0.92	5.62±0.96	5.83±1.00
Non-HDL-cholesterol, mmol/L	3.80±0.95	3.85±0.90	4.19±0.95	4.55±1.00
Medication use for dyslipidemia, %	3.0	1.4	4.2	6.8
Fasting blood glucose, mmol/L	5.25±0.84	5.03±0.33	5.45±0.91	6.29±1.56
Non-fasting blood glucose, mmol/L	5.91±1.59	5.63±0.71	6.22±1.88	7.13±2.41
Medication use for diabetes, %	1.2	0	1.8	7.6
Hypertensives, %	38.3	0	66.5	89.5
Dyslipidemia, %	16.5	0	31.2	70.9

Diabetes, %	2.5	0	3.8	16.6
Age, 65-74 y				
Men				
No. of participants	1,521	95	1,146	
Age, y	69.0±2.8	69.0±2.9	68.7±2.8	
Current smokers, %	43.9	39.4	31.9	
Waist circumference, cm	76.7±5.6	89.0±4.6	90.5±5.3	
Body mass index, kg/m^2	21.0±2.1	24.3±2.3	25.2±2.2	
Systolic blood pressure, mmHg	134.0±19.8	118.7±7.7	140.3±17.7	
Diastolic blood pressure, mmHg	77.4±11.1	72.5±7.7	82.0±10.3	
Medication use for hypertension, %	19.3	0.0	32.8	
Triglycerides, mmol/L	1.26±0.73	1.11±0.31	1.85±1.11	
HDL-cholesterol, mmol/L	1.44±0.40	1.38±0.29	1.25±0.33	
Total cholesterol, mmol/L	4.94±0.91	4.90±0.80	5.16±0.88	
Non-HDL-cholesterol, mmol/L	3.49±0.91	3.52±0.82	3.91±0.88	
Medication use for dyslipidemia, %	2.0	0.0	5.8	
Fasting blood glucose, mmol/L	5.64±1.45	5.12±0.29	6.01±1.33	
Non-fasting blood glucose, mmol/L	6.53±2.29	5.90±0.84	6.93±2.37	
Medication use for diabetes, %	4.1	0	7.8	
Hypertensives, %	64.7	0	81.1	
Dyslipidemia, %	25.7	0	54.4	
Diabetes, %	8.1	0	14.0	

Women

No. of participants	2523	115	1,286
Age, y	69.0±2.8	68.8±2.7	69.0±2.8
Current smokers, %	6.0	2.6	5.1
Waist circumference, cm	76.9±7.5	90.9±6.2	91.4±7.5
Body mass index, kg/m^2	21.5±2.2	25.9±2.0	26.9±2.5
Systolic blood pressure, mmHg	133.9±19.8	118.2±8.1	143.0±18.1
Diastolic blood pressure, mmHg	75.8±10.6	71.1±7.2	81.2±10.3
Medication use for hypertension, %	22.2	0.0	40.8
Triglycerides, mmol/L	1.39±0.82	1.15±0.31	1.73±0.90
HDL-cholesterol, mmol/L	1.51±0.38	1.54±0.33	1.36±0.34
Total cholesterol, mmol/L	5.62±0.95	5.52±0.77	5.71±0.90
Non-HDL-cholesterol, mmol/L	4.10±0.97	3.97±0.76	4.34±0.92
Medication use for dyslipidemia, %	6.9	6.1	7.9
Fasting blood glucose, mmol/L	5.43±0.93	5.06±0.31	5.71±1.13
Non-fasting blood glucose, mmol/L	6.05±1.62	5.77±0.74	6.62±2.39
Medication use for diabetes, %	3.0	0	6.1
Hypertensives, %	63.9	0	86.9
Dyslipidemia, %	26.4	0	44.0
Diabetes, %	4.7	0	9.6

ISO, information supply only; MSI, motivation-support intervention; ISI, intensive support intervention. For ages of 65-74 years, the ISI was collapsed into MSI.

Table S4. Age- and Sex-specific Risk Characteristics According to the Refined Category of Health Intervention with Nonobese/overweight and Referral Subtypes for Screened Participants.

	Nonobese/overweight			Obesity/overweight: lifestyle intervention			
	Super normal (reference)	Nonobese/ overweight and no need for referral	Nonobese/ overweight and need for referral	ISO	MSI		ISI	
	Waist <85cm in men /<90cm in women and BMI <25 kg/m^2, and 0 risk factor	Waist <85cm in men/<90cm in women and BMI <25kg/m^2, and no referral risk levels	Waist <85cm in men/<90 cm in women and BMI <25kg/m^2, and referral risk levels	Waist ≥85cm in men/≥90cm in women and 0 risk factor OR Waist <85cm in men/ <90cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥85cm in men/ ≥90cm in women and 1 risk factor OR Waist <85cm in men/ <90cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors		Waist ≥85cm in men/≥90cm in women and ≥2 risk factors OR Waist <85cm in men/<90cm in women and BMI ≥25 kg/m^2, and ≥3 risk factors	
					Plus no referral risk levels	Plus referral risk levels	Plus no referral risk levels	Plus referral risk levels
Age, 40-64 y								
Men								
No. of participants	1,747	1,519	2,177	588	445	630	745	2,644
Age, y	49.6±6.9	50.5±6.8	53.1±6.9	49.9±6.7	51.0±6.6	52.2±6.9	51.4±7.1	52.4±6.8
Current smokers, %	55.4	54.4	51.1	46.7	5.9	7.2	66.7	51.9
Waist circumference, cm	75.9±5.3	77.7±4.7	78.5±4.6	87.8±4.3	87.9±4.9	88.6±5.8	90.0±4.7	91.1±5.7
Body mass index, kg/m^2	21.4±1.9	21.7±1.8	22.1±1.8	25.3±1.9	25.5±1.9	25.9±2.0	26.5±2.3	26.3±2.6
Systolic blood pressure, mmHg	113.5±9.1	122.6±11.4	135.2±18.1	115.9±8.3	122.6±9.8	132.9±18.1	126.2±9.9	138.1±17.1
Diastolic blood pressure, mmHg	71.4±7.3	76.5±8.3	84.0±11.5	73.8±6.7	77.9±6.7	84.6±11.3	78.7±7.4	87.0±10.8
Medication use for hypertension, %	0	0	19.5	0	0	21.6	0	27.8

Triglycerides, mmol/L	0.97±0.32	1.38±0.70	1.84±1.54	1.12±0.31	1.40±0.61	1.65±1.16	1.72±0.66	2.44±1.63
HDL-cholesterol, mmol/L	1.52±0.35	1.46±0.38	1.37±0.41	1.38±0.26	1.37±0.30	1.32±0.33	1.27±0.28	1.20±0.31
Total cholesterol, mmol/L	4.99±0.82	4.88±0.70	5.37±1.00	5.17±0.81	5.03±0.65	5.46±0.88	4.94±0.65	5.50±0.94
Non-HDL-cholesterol, mmol/L	3.46±0.83	3.42±0.69	4.01±1.02	3.79±0.80	3.66±0.65	4.14±0.89	3.67±0.67	4.30±0.92
Medication use for dyslipidemia, %	0.7	0	4.2	1.7	0	4.6	0	6.2
Fasting blood glucose, mmol/L	4.96±0.37	5.46±0.55	5.890±1.62	5.06±0.33	5.46±0.45	5.50±1.05	5.63±0.52	6.19±1.56
Non-fasting blood glucose, mmol/L	5.66±0.82	6.35±1.57	7.21±3.07	5.82±0.87	6.04±1.02	6.13±1.13	6.61±1.52	7.54±3.06
Medication use for diabetes, %	0	0	5.7	0	0	2.2	0	6.3
Hypertensives, %	0	46.2	72.9	0	35.3	61.4	58.5	80.8
Dyslipidemia, %	0	40.0	47.3	0	33.9	30.0	61.9	73.6
Diabetes, %	0	0	14.1	0	0	6.2	0	17.3
Women								
No. of participants	4,372	1,806	2,598	806	579	1,064	149	733
Age, y	49.9±6.7	52.5±6.8	55.2±6.2	51.4±6.9	52.4±6.9	54.5±6.5	54.3±6.5	55.8±6.1
Current smokers, %	6.4	7.0	6.2	5.9	2.1	2.0	25.7	11.1
Waist circumference, cm	73.7±7.1	75.8±7.0	77.1±7.0	86.8±8.0	87.9±6.8	87.5±7.7	94.4±6.0	94.6±6.7
Body mass index, kg/m^2	21.3±2.0	21.8±1.9	22.2±1.9	26.4±1.9	26.8±2.0	27.1±2.4	27.3±2.8	28.0±3.1
Systolic blood pressure, mmHg	111.1±9.9	122.7±12.4	137.0±18.6	114.9±8.9	123.4±11.0	138.3±18.4	128.0±9.7	142.4±16.1
Diastolic blood pressure, mmHg	68.9±7.6	74.5±8.5	82.0±11.1	71.7±7.3	75.7±7.8	84.1±11.1	78.7±7.1	85.2±10.4
Medication use for hypertension, %	0	0	29.6	0	0	33.4	0	43.2
Triglycerides, mmol/L	0.89±0.31	1.25±0.64	1.51±1.40	1.01±0.33	1.45±0.68	1.49±0.97	1.81±0.61	2.10±1.23
HDL-cholesterol, mmol/L	1.64±0.34	1.55±0.37	1.47±0.39	1.53±0.31	1.44±0.33	1.42±0.33	1.31±0.28	1.27±0.30
Total cholesterol, mmol/L	5.22±0.89	5.17±0.80	5.77±0.98	5.38±0.92	5.25±0.80	5.82±0.98	5.38±0.91	5.92±0.99
Non-HDL-cholesterol, mmol/L	3.57±0.97	3.62±0.79	4.30±1.00	3.85±0.90	3.81±0.79	4.40±0.96	4.07±0.91	4.65±0.98

Medication use for dyslipidemia, %	1.1	0	8.2	1.4	0	6.5	0	8.2
Fasting blood glucose, mmol/L	4.95±0.32	5.41±0.51	5.63±1.28	5.03±0.33	5.43±0.53	5.46±1.02	5.80±0.44	6.36±1.65
Non-fasting blood glucose, mmol/L	5.52±0.76	5.99±1.19	6.56±2.61	5.63±0.71	6.09±1.10	6.36±2.44	6.48±1.53	7.40±2.65
Medication use for diabetes	0	0	19.6	0	0	2.7	0	9.1
Hypertensives, %	0	49.4	79.9	0	46.3	77.4	74.5	92.5
Dyslipidemia, %	0	31.9	33.6	0	38.9	27.1	73.2	70.4
Diabetes, %	0	0	8.6	0	0	5.8	0	19.9

Age, 65-74 y

Men

No. of participants	301	385	835	95	224	922
Age, y	69.0±2.7	68.8±2.9	69.0±2.8	69.0±2.9	68.7±2.9	68.7±2.7
Current smokers, %	46.0	42.3	43.8	39.4	33.9	31.4
Waist circumference, cm	74.6±5.6	76.7±5.6	77.4±5.3	89.0±4.6	90.0±5.2	90.6±5.3
Body mass index, kg/m^2	20.3±2.0	21.0±2.0	21.2±2.0	24.3±2.3	25.0±2.1	25.3±2.2
Systolic blood pressure, mmHg	114.0±10.1	126.2±11.1	144.8±18.2	118.7±7.7	126.6±9.6	143.6±17.6
Diastolic blood pressure, mmHg	69.2±8.2	74.3±8.0	81.8±11.1	72.5±7.6	76.3±7.1	83.4±10.5
Medication use for hypertension, %	0	0	35.2	0	0	40.8
Triglycerides, mmol/L	0.96±0.31	1.22±0.59	1.38±0.85	1.11±0.31	1.62±0.71	1.90±1.18
HDL-cholesterol, mmol/L	1.53±0.34	1.43±0.39	1.42±0.42	1.38±0.29	1.31±0.32	1.23±0.33
Total cholesterol, mmol/L	4.90±0.84	4.77±0.78	5.03±0.97	4.90±0.80	5.01±0.72	5.20±0.91
Non-HDL-cholesterol, mmol/L	3.37±0.84	3.35±0.77	3.61±0.97	3.52±0.82	3.70±0.67	3.97±0.92
Medication use for dyslipidemia, %	2.0	0	3.0	0	0	7.3
Fasting blood glucose, mmol/L	5.02±0.31	5.51±0.55	5.90±1.83	5.12±0.29	5.68±0.55	6.08±1.43

Non-fasting blood glucose, mmol/L	5.43±0.81	6.19±1.40	7.14±2.84	5.90±0.84	6.39±1.40	7.09±2.56
Medication use for diabetes, %	0	0	7.4	0	0	9.7
Hypertensives, %	0	60.8	89.8	0	54.5	87.5
Dyslipidemia, %	0	31.9	32.1	0	49.1	55.6
Diabetes, %	0	0	14.7	0	0	17.4
Women						
No. of participants	566	534	1423	115	231	1,055
Age, y	68.7±2.8	68.7±2.7	69.2±2.8	68.8±2.7	68.6±2.8	69.1±2.8
Current smokers, %	7.1	6.4	5.5	2.6	4.4	5.2
Waist circumference, cm	74.9±7.9	77.0±7.4	77.7±7.2	90.9±6.2	91.6±7.0	91.3±7.6
Body mass index, kg/m^2	20.7±2.4	21.4±2.1	21.8±2.1	25.9±2.0	26.3±2.2	27.0±2.5
Systolic blood pressure, mmHg	114.9±9.9	126.6±11.5	144.2±18.3	118.2±8.1	127.4±9.9	146.4±17.7
Diastolic blood pressure, mmHg	69.1±8.0	73.4±8.1	79.4±10.8	71.1±7.2	75.7±7.4	82.5±10.4
Medication use for hypertension, %	0	0	39.4	0	0	49.8
Triglycerides, mg/dl	1.04±0.30	1.43±0.64	1.51±0.98	1.15±0.31	1.63±0.65	1.75±0.94
HDL-cholesterol, mg/dl	1.62±0.34	1.52±0.36	1.47±0.40	1.54±0.33	1.36±0.30	1.36±0.35
Total cholesterol, mmol/L	5.50±0.94	5.45±0.85	5.73±0.98	5.52±0.77	5.51±0.87	5.75±0.90
Non-HDL-cholesterol, mmol/L	3.89±0.93	3.93±0.85	4.25±1.00	3.97±0.76	4.14±0.85	4.39±0.92
Medication use for dyslipidemia, %	6.7	0	9.5	6.1	0	9.7
Fasting blood glucose, mmol/L	5.01±0.29	5.43±0.55	5.57±1.09	5.06±0.31	5.40±0.51	5.74±1.18
Non-fasting blood glucose, mmol/L	5.46±0.77	5.94±1.08	6.40±2.04	5.77±0.74	6.23±1.27	6.76±2.66
Medication use for diabetes, %	0	0	5.4	0	0	7.4
Hypertensives, %	0	64.6	89.0	0	59.7	92.8
Dyslipidemia, %	0	38.2	32.5	0	47.2	43.3

Diabetes, %	0	0	8.3	0	0	11.8

ISO, information supply only; MSI, motivation-support intervention; ISI, intensive support intervention. Referral risk levels were defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or medication use; triglycerides level ≥3.39mmol/L (300mg/dL) and/or high-density lipoprotein (HDL) cholesterol level ≤0.91mmol/L (34mg/dL) or non-HDL-cholesterol level ≥4.40mmol/L (170mg/dL) or medication use; fasting glucose level≥7.0mmol/L (126mg/dL) or non-fasting glucose level ≥1.11mmol/L (200mg/dL) or medication use.

For ages of 65-74 years, the ISI was collapsed into MSI.

Table S5. Age- and Sex-specific Risk Characteristics According to the Refined Category of Health Intervention with Nonobese/overweight and Referral Subtypes for Screened Participants.

	Nonobese/overweight			Obesity/overweight: lifestyle intervention				
	Super normal (reference)	Nonobese/ overweight and no need for referral	Nonobese/ overweight and need for referral	ISO	MSI		ISI	
	Waist <85cm in men/ <90cm in women and BMI <25 kg/m^2, and 0 risk factor	Waist <85cm in men/<90cm in women and BMI <25kg/m^2, and no referral risk levels	Waist <85cm in men/<90 cm in women and BMI <25kg/m^2, and referral risk levels	Waist ≥85cm in men/≥90cm in women and 0 risk factor OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥85cm in men/≥90cm in women and 1 risk factor OR Waist <85cm in men/ <90cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors		Waist ≥85cm in men/≥90cm in women and ≥2 risk factors OR Waist <85cm in men/<90cm in women and BMI ≥25 kg/m^2, and ≥3 risk factors	
					Plus no referral risk levels	Plus referral risk levels	Plus no referral risk levels	Plus referral risk levels
Age, 40-64 y								
Men								
No. of participants	1,747	1,519	2,177	588	445	630	745	2,644
Age, y	49.6±6.9	50.5±6.8	53.1±6.9	49.9±6.7	51.0±6.6	52.2±6.9	51.4±7.1	52.4±6.8
Current smokers, %	55.4	54.4	51.1	46.7	5.9	7.2	66.7	51.9
Waist circumference, cm	75.9±5.3	77.7±4.7	78.5±4.6	87.8±4.3	87.9±4.9	88.6±5.8	90.0±4.7	91.1±5.7
Body mass index, kg/m^2	21.4±1.9	21.7±1.8	22.1±1.8	25.3±1.9	25.5±1.9	25.9±2.0	26.5±2.3	26.3±2.6
Systolic blood pressure, mmHg	113.5±9.1	122.6±11.4	135.2±18.1	115.9±8.3	122.6±9.8	132.9±18.1	126.2±9.9	138.1±17.1
Diastolic blood pressure, mmHg	71.4±7.3	76.5±8.3	84.0±11.5	73.8±6.7	77.9±6.7	84.6±11.3	78.7±7.4	87.0±10.8
Medication use for hypertension, %	0	0	19.5	0	0	21.6	0	27.8

Triglycerides, mmol/L	0.97±0.32	1.38±0.70	1.84±1.54	1.12±0.31	1.40±0.61	1.65±1.16	1.72±0.66	2.44±1.63
HDL-cholesterol, mmol/L	1.52±0.35	1.46±0.38	1.37±0.41	1.38±0.26	1.37±0.30	1.32±0.33	1.27±0.28	1.20±0.31
Total cholesterol, mmol/L	4.99±0.82	4.88±0.70	5.37±1.00	5.17±0.81	5.03±0.65	5.46±0.88	4.94±0.65	5.50±0.94
Non-HDL-cholesterol, mmol/L	3.46±0.83	3.42±0.69	4.01±1.02	3.79±0.80	3.66±0.65	4.14±0.89	3.67±0.67	4.30±0.92
Medication use for dyslipidemia, %	0.7	0	4.2	1.7	0	4.6	0	6.2
Fasting blood glucose, mmol/L	4.96±0.37	5.46±0.55	5.890±1.62	5.06±0.33	5.46±0.45	5.50±1.05	5.63±0.52	6.19±1.56
Non-fasting blood glucose, mmol/L	5.66±0.82	6.35±1.57	7.21±3.07	5.82±0.87	6.04±1.02	6.13±1.13	6.61±1.52	7.54±3.06
Medication use for diabetes, %	0	0	5.7	0	0	2.2	0	6.3
Hypertensives, %	0	46.2	72.9	0	35.3	61.4	58.5	80.8
Dyslipidemia, %	0	40.0	47.3	0	33.9	30.0	61.9	73.6
Diabetes, %	0	0	14.1	0	0	6.2	0	17.3
Women								
No. of participants	4,372	1,806	2,598	806	579	1,064	149	733
Age, y	49.9±6.7	52.5±6.8	55.2±6.2	51.4±6.9	52.4±6.9	54.5±6.5	54.3±6.5	55.8±6.1
Current smokers, %	6.4	7.0	6.2	5.9	2.1	2.0	25.7	11.1
Waist circumference, cm	73.7±7.1	75.8±7.0	77.1±7.0	86.8±8.0	87.9±6.8	87.5±7.7	94.4±6.0	94.6±6.7
Body mass index, kg/m^2	21.3±2.0	21.8±1.9	22.2±1.9	26.4±1.9	26.8±2.0	27.1±2.4	27.3±2.8	28.0±3.1
Systolic blood pressure, mmHg	111.1±9.9	122.7±12.4	137.0±18.6	114.9±8.9	123.4±11.0	138.3±18.4	128.0±9.7	142.4±16.1
Diastolic blood pressure, mmHg	68.9±7.6	74.5±8.5	82.0±11.1	71.7±7.3	75.7±7.8	84.1±11.1	78.7±7.1	85.2±10.4
Medication use for hypertension, %	0	0	29.6	0	0	33.4	0	43.2
Triglycerides, mmol/L	0.89±0.31	1.25±0.64	1.51±1.40	1.01±0.33	1.45±0.68	1.49±0.97	1.81±0.61	2.10±1.23
HDL-cholesterol, mmol/L	1.64±0.34	1.55±0.37	1.47±0.39	1.53±0.31	1.44±0.33	1.42±0.33	1.31±0.28	1.27±0.30
Total cholesterol, mmol/L	5.22±0.89	5.17±0.80	5.77±0.98	5.38±0.92	5.25±0.80	5.82±0.98	5.38±0.91	5.92±0.99
Non-HDL-cholesterol, mmol/L	3.57±0.97	3.62±0.79	4.30±1.00	3.85±0.90	3.81±0.79	4.40±0.96	4.07±0.91	4.65±0.98

Medication use for dyslipidemia, %	1.1	0	8.2	1.4	0	6.5	0	8.2
Fasting blood glucose, mmol/L	4.95±0.32	5.41±0.51	5.63±1.28	5.03±0.33	5.43±0.53	5.46±1.02	5.80±0.44	6.36±1.65
Non-fasting blood glucose, mmol/L	5.52±0.76	5.99±1.19	6.56±2.61	5.63±0.71	6.09±1.10	6.36±2.44	6.48±1.53	7.40±2.65
Medication use for diabetes	0	0	19.6	0	0	2.7	0	9.1
Hypertensives, %	0	49.4	79.9	0	46.3	77.4	74.5	92.5
Dyslipidemia, %	0	31.9	33.6	0	38.9	27.1	73.2	70.4
Diabetes, %	0	0	8.6	0	0	5.8	0	19.9

Age, 65-74 y

Men

No. of participants	301	385	835	95	224	922
Age, y	69.0±2.7	68.8±2.9	69.0±2.8	69.0±2.9	68.7±2.9	68.7±2.7
Current smokers, %	46.0	42.3	43.8	39.4	33.9	31.4
Waist circumference, cm	74.6±5.6	76.7±5.6	77.4±5.3	89.0±4.6	90.0±5.2	90.6±5.3
Body mass index, kg/m^2	20.3±2.0	21.0±2.0	21.2±2.0	24.3±2.3	25.0±2.1	25.3±2.2
Systolic blood pressure, mmHg	114.0±10.1	126.2±11.1	144.8±18.2	118.7±7.7	126.6±9.6	143.6±17.6
Diastolic blood pressure, mmHg	69.2±8.2	74.3±8.0	81.8±11.1	72.5±7.6	76.3±7.1	83.4±10.5
Medication use for hypertension, %	0	0	35.2	0	0	40.8
Triglycerides, mmol/L	0.96±0.31	1.22±0.59	1.38±0.85	1.11±0.31	1.62±0.71	1.90±1.18
HDL-cholesterol, mmol/L	1.53±0.34	1.43±0.39	1.42±0.42	1.38±0.29	1.31±0.32	1.23±0.33
Total cholesterol, mmol/L	4.90±0.84	4.77±0.78	5.03±0.97	4.90±0.80	5.01±0.72	5.20±0.91
Non-HDL-cholesterol, mmol/L	3.37±0.84	3.35±0.77	3.61±0.97	3.52±0.82	3.70±0.67	3.97±0.92
Medication use for dyslipidemia, %	2.0	0	3.0	0	0	7.3
Fasting blood glucose, mmol/L	5.02±0.31	5.51±0.55	5.90±1.83	5.12±0.29	5.68±0.55	6.08±1.43

Non-fasting blood glucose, mmol/L	5.43±0.81	6.19±1.40	7.14±2.84	5.90±0.84	6.39±1.40	7.09±2.56
Medication use for diabetes, %	0	0	7.4	0	0	9.7
Hypertensives, %	0	60.8	89.8	0	54.5	87.5
Dyslipidemia, %	0	31.9	32.1	0	49.1	55.6
Diabetes, %	0	0	14.7	0	0	17.4
Women						
No. of participants	566	534	1423	115	231	1,055
Age, y	68.7±2.8	68.7±2.7	69.2±2.8	68.8±2.7	68.6±2.8	69.1±2.8
Current smokers, %	7.1	6.4	5.5	2.6	4.4	5.2
Waist circumference, cm	74.9±7.9	77.0±7.4	77.7±7.2	90.9±6.2	91.6±7.0	91.3±7.6
Body mass index, kg/m^2	20.7±2.4	21.4±2.1	21.8±2.1	25.9±2.0	26.3±2.2	27.0±2.5
Systolic blood pressure, mmHg	114.9±9.9	126.6±11.5	144.2±18.3	118.2±8.1	127.4±9.9	146.4±17.7
Diastolic blood pressure, mmHg	69.1±8.0	73.4±8.1	79.4±10.8	71.1±7.2	75.7±7.4	82.5±10.4
Medication use for hypertension, %	0	0	39.4	0	0	49.8
Triglycerides, mg/dl	1.04±0.30	1.43±0.64	1.51±0.98	1.15±0.31	1.63±0.65	1.75±0.94
HDL-cholesterol, mg/dl	1.62±0.34	1.52±0.36	1.47±0.40	1.54±0.33	1.36±0.30	1.36±0.35
Total cholesterol, mmol/L	5.50±0.94	5.45±0.85	5.73±0.98	5.52±0.77	5.51±0.87	5.75±0.90
Non-HDL-cholesterol, mmol/L	3.89±0.93	3.93±0.85	4.25±1.00	3.97±0.76	4.14±0.85	4.39±0.92
Medication use for dyslipidemia, %	6.7	0	9.5	6.1	0	9.7
Fasting blood glucose, mmol/L	5.01±0.29	5.43±0.55	5.57±1.09	5.06±0.31	5.40±0.51	5.74±1.18
Non-fasting blood glucose, mmol/L	5.46±0.77	5.94±1.08	6.40±2.04	5.77±0.74	6.23±1.27	6.76±2.66
Medication use for diabetes, %	0	0	5.4	0	0	7.4
Hypertensives, %	0	64.6	89.0	0	59.7	92.8
Dyslipidemia, %	0	38.2	32.5	0	47.2	43.3

Diabetes, %	0	0	8.3	0	0	11.8

ISO, information supply only; MSI, motivation-support intervention; ISI, intensive support intervention. Referral risk levels were defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or medication use; triglycerides level ≥3.39mmol/L (300mg/dL) and/or high-density lipoprotein (HDL) cholesterol level ≤0.91mmol/L (34mg/dL) or non-HDL-cholesterol level ≥4.40mmol/L (170mg/dL) or medication use; fasting glucose level ≥7.0mmol/L (126mg/dL) or non-fasting glucose level ≥1.11mmol/L (200mg/dL) or medication use.
For ages of 65-74 years, the ISI was collapsed into MSI.

Table S6. Age- and Sex-specific HRs of Total CVD According to the Legislated Category of Health Intervention for Screened Participants Without Medication Use for Hypertension, Diabetes, and Dyslipidemia.

		Obese/overweight: lifestyle intervention		
	Nonobese/overweight (reference)	ISO	MSI	ISI
	Waist <85cm in men/<90cm in women and BMI <25kg/m^2, regardless of risk factor	Waist ≥85cm in men/ ≥90cm in women and 0 risk factor OR Waist <85cm in men/ <90cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥85cm in men/≥90cm in women and 1 risk factor OR Waist<85cm in men/<90cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors	Waist ≥85cm in men/≥90cm in women and ≥2 risk factors OR Waist <85cm in men/<90cm in women and BMI ≥25 kg/m^2, and ≥3 risk factors
Age, 40-64 y				
Men, n	4,864	578	913	2,534
No. of patient-years	43,405	4,950	7,455	20,205
No. of cases	100	8	17	98
Age- and area-adjusted HR (95%CI)	1.00	0.82 (0.40-1.68)	0.99 (0.59-1.66)	1.82 (1.37-2.42)
Multivariable HR (95%CI)	1.00	0.80 (0.39-1.66)	0.97 (0.58-1.63)	1.73 (1.29-2.32)
PAF (95%CI)		-	-	18.5 (7.4-28.3)
Women, n	7,791	795	1,237	525
No. of patient-years	72,495	7,746	12,222	4,979
No. of cases	98	3	15	18
Age and area-adjusted HR (95%CI)	1.00	0.31 (0.10-0.96)	0.85 (0.49-1.46)	2.03 (1.22-3.40)
Multivariable HR (95%CI)	1.00	0.31 (0.10-0.97)	0.87 (0.50-1.52)	2.13 (1.26-3.59)
PAF (95%CI)		-	-	7.1 (0.6-13.2)

Age, 65-74 y			
Men, n	1,170	95	701
No. of patient-years	9,787	785	5,250
No. of cases	95	6	57
Age and area-adjusted HR (95%CI)	1.00	0.80 (0.35-1.82)	1.15 (0.83-1.61)
Multivariable HR (95%CI)	1.00	0.80 (0.35-1.82)	1.15 (0.81-1.61)
PAF (95%CI)		-	-
Women, n	1,823	108	694
No. of patient-years	15,889	923	5,919
No. of cases	86	3	43
Age and area-adjusted HR (95%CI)	1.00	0.71 (0.22-2.26)	1.34 (0.93-1.93)
Multivariable HR (95%CI)	1.00	0.72 (0.23-2.29)	1.32 (0.91-1.91)
PAF (95%CI)		-	-

ISO, information supply only; MSI, motivation-support intervention; ISI, intensive support intervention. Multivariable hazard ratio (HR): adjusted further for non-high-density lipoprotein (HDL) cholesterol.
For ages of 65-74 years, the ISI was collapsed into MSI.

Table S7. Age- and Sex-specific HRs of Total CVD According to the Refined Category of Health Intervention With Nonobese/overweight and Referral Subtypes for Screened Participants Without Medication Use for Hypertension, Diabetes, and Dyslipidemia.

	Nonobese/overweight			Obese/overweight: lifestyle intervention			
	Super normal (reference)	Nonobese/ overweight and no need for referral	Non-obese/ overweight and need for referral	ISO	MSI		ISI	
	Waist <85cm in men/ <90cm in women and BMI <25 kg/m^2, and 0 risk factor	Waist <85cm in men/<90cm in women and BMI <25kg/m^2 , and no referral risk levels	Waist <85cm in men/<90 cm in women and BMI <25kg/m^2 and referral risk levels	Waist ≥85cm in men/≥90cm in women and 0 risk factor OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥85cm in men/≥90cm in women and 1 risk factor OR Waist <85cm in men/ <90cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors		Waist ≥85cm in men/≥90cm in women and ≥2 risk factors OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and ≥3 risk factors	
					Plus no referral risk levels	Plus referral risk levels	Plus no referral risk levels	Plus referral risk levels
Age, 40-64 y								
Men, n	1,735	1,519	1,610	578	445	468	745	1,789
No. of patient-years	16,139	13,392	13,874	4,950	3,914	3,541	6,110	14,094
No. of cases	22	15	63	8	4	13	15	83
Age and area-adjusted HR (95%CI)	1.00	0.77 (0.40-1.49)	2.63 (1.61-4.31)	1.22 (0.54-2.75)	0.68 (0.23-1.97)	2.33 (1.17-4.65)	1.49 (0.77-2.88)	3.40 (2.11-5.48)
Multivariable HR (95%CI)	1.00	0.77 (0.40-1.489	2.69 (1.63-4.42)	1.24 (0.55-2.79)	0.68 (0.23-1.98)	2.38 (1.19-4.78)	1.50 (0.77-2.92)	3.50 (2.14-5.74)
PAF (95%CI)		-	17.7 (9.4-25.4)	-	-	3.4 (0.0-6.6)	-	26.6 (17.4-34.7)
Women, n	4,325	1,806	1,660	795	579	658	149	376
No. of patient-years	39,443	17,853	15,199	7,746	5,995	6,228	1,534	3,445
No. of cases	27	27	44	3	7	8	4	14
Age and area-adjusted	1.00	2.10 (1.22-3.60)	2.79 (1.70-4.60)	0.53 (0.16-1.75)	1.84 (0.80-4.27)	1.32 (0.60-2.93)	3.47 (1.20-10.1)	3.85 (1.98-7.51)
Multivariable HR (95%CI)	1.00	2.07 (1.21-3.55)	3.14 (1.88-5.24)	0.55 (0.17-1.83)	1.88 (0.81-4.36)	1.54 (0.68-3.47)	3.60 (1.24-10.4)	4.56 (2.28-9.10)

PAF (95%CI)		9.9 (1.7-17.4)	21.3 (11.2-30.2)	-	-	-	2.1 (0.0-4.8)	7.8 (2.5-12.7)
Age, 65-74 y								
Men, n	295	385	490	95	224	477		
No. of patient-years	2,543	3,332	3,911	785	1,764	3,486		
No. of cases	14	24	57	6	11	46		
Age and area-adjusted HR (95%CI)	1.00	1.46 (0.75-2.82)	2.61 (1.45-4.69)	1.46 (0.56-3.80)	1.30 (0.59-2.87)	2.49 (1.36-2.87)		
Multivariable HR (95%CI)	1.00	1.46 (0.76-2.83)	2.68 (1.49-4.84)	1.48 (0.57-3.86)	1.33 (0.60-2.95)	2.60 (1.41-4.80)		
PAF (95%CI)		-	22.6 (11.6-32.3)	-	-	17.9 (7.3-27.3)		
Women, n	528	534	761	108	231	463		
No. of patient-years	4,485	4,810	6,594	923	1,764	3,486		
No. of cases	15	27	44	3	14	29		
Age and area-adjusted HR (95%CI)	1.00	1.71 (0.92-3.26)	1.83 (1.01-3.32)	1.09 (0.31-3.76)	2.08 (1.00-4.31)	2.19 (1.17-4.10)		
Multivariable HR (95%CI)	1.00	1.73 (0.92-3.26)	1.81 (0.99-3.30)	1.09 (0.31-3.77)	2.07 (1.00-4.29)	2.16 (1.14-4.08)		
PAF (95%CI)		-	-	-	5.5 (0.0-11.4)	11.8 (1.90-20.7)		

ISO, information supply only; MSI, motivation-support intervention; ISI, intensive support intervention. Referral risk levels were defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or medication use; triglycerides level ≥3.39mmol/L (300mg/dL) and/or high-density lipoprotein (HDL) cholesterol level ≤0.91mmol/L (34mg/dL) or non-HDL-cholesterol level ≥4.40mmol/L (170mg/dL) or medication use; fasting glucose level ≥7.0mmol/L (126mg/dL) or non-fasting glucose level ≥1.11mmol/L (200mg/dL) or medication use. Multivariable hazard ratio (HR): adjusted further for non-HDL-cholesterol.
For ages of 65-74 years, the ISI was collapsed into MSI.

Table S8. Age- and Sex-specific HRs of Total CVD According to the Legislated Category of Health Intervention for Screened Participants Based on the Asian Cutoff of Waist Circumference*.

		Obese/overweight: lifestyle intervention		
	Non-obese/ overweight (reference)	ISO	MSI	ISI
	Waist <90cm in men/<80cm in women and BMI <25kg/m^2, regardless of risk factor	Waist ≥90cm in men /≥80cm in women and 0 risk factor OR Waist <90cm in men/ <80cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥90cm in men/≥80cm in women and 1 risk factor OR Waist <90cm in men/ <80cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors	Waist ≥90cm in men/≥80cm in women and ≥2 risk factors OR Waist <90cm in men/ <80cm in women and BMI ≥25 kg/m^2, and ≥3 risk factors
Age, 40-64 y				
Men, n	6,857	371	1,162	2,105
No. of patient-y	59,488	3,140	9,058	15,702
No. of cases	181	5	31	110
Age and area-adjusted HR (95%CI)	1.00	0.69 (0.28-1.67)	1.12 (0.76-1.64)	2.01 (1.58-2.56)
Multivariable HR (95%CI)	1.00	0.68 (0.28-1.65)	1.09 (0.74-1.60)	1.91 (1.49-2.44)
PAF (95%CI)		-	-	16.0 (9.1-22.4)
Women, n	6,147	1,786	2,296	1,878
No. of patient-y	56,489	16,809	22,014	16,945
No. of cases	94	10	43	61
Age and area-adjusted HR (95%CI)	1.00	0.37 (0.19-0.71)	1.05 (0.73-1.51)	1.45 (1.03-2.02)
Multivariable HR (95%CI)	1.00	0.37 (0.19-0.71)	1.08 (0.74-1.56)	1.52 (1.08-2.16)
PAF (95%CI)		-	-	10.0 (1.0-18.2)

Age, 65-74 years			
Men, n	1,970	47	745
No. of patient-y	15,997	386	5,516
No. of cases	171	1	66
Age and area-adjusted HR (95%CI)	1.00	-	1.13 (0.85-1.51)
Multivariable HR (95%CI)	1.00	-	1.13 (0.85-1.52)
PAF (95%CI)		-	-
Women, n	1,498	295	2,131
No. of patient-y	12,973	2,504	18,133
No. of cases	81	8	161
Age and area-adjusted HR (95%CI)	1.00	0.60 (0.29-1.24)	1.43 (1.10-1.87)
Multivariable HR (95%CI)	1.00	0.60 (0.29-1.24)	1.43 (1.09-1.88)
PAF (95%CI)		-	19.4 (4.1-32.2)

*Waist cutoff values using 90cm for men and 80cm for women. ISO, information supply only; MSI, motivation-support intervention; ISI, intensive support intervention. Multivariable hazard ratio (HR): adjusted further for non-high-density lipoprotein (HDL) cholesterol.
For ages of 65-74 years, the ISI was collapsed into MSI.

Table S9. Age- and Sex-specific HRs of Total CVD According to the Refined Category of Health Intervention With Nonobese/overweight and Referral Subtypes for Screened Participants Based on the Asian Cutoff of Waist circumference*.

	Nonobese/overweight			Obese/overweight: lifestyle intervention			
	Super Normal (reference)	Nonobese/ overweight and no need for referral	Nonobese/ overweight and need for referral	ISO	MSI		ISI	
	Waist <85cm in men, <90cm in women and BMI <25kg/m^2, and 0 risk factor	Waist <85cm in men/<90cm in women and BMI <25kg/m^2 and no referral risk levels	Waist <85cm in men/<90cm in women and BMI <25kg/m^2 and referral risk levels	Waist ≥85cm in men/≥90cm in women and 0 risk factor OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and 0 risk factor	Waist ≥85cm in men/≥90cm in women and 1 risk factor OR Waist <85cm in men/<90cm in women and BMI ≥25kg/m^2, and 1 or 2 risk factors		Waist ≥85cm in men/≥90cm in women and ≥2 risk factors OR Waist<85cm in men/<90cm in women and BMI ≥25 kg/m^2, and ≥3 risk factors	
					Plus no referral risk levels	Plus referral risk levels	Plus no referral risk levels	Plus referral risk levels
Age, 40-64 y								
Men, n	1,964	1,915	2,978	371	414	748	380	1725
No. of patient-y	18,106	16,874	24,508	3,140	3536	5,522	3007	12,695
No. of cases	25	22	134	5	4	27	8	102
Age and area-adjusted HR (95%CI)	1.00	0.86 (0.48-1.52)	2.84 (1.84-4.37)	1.22 (0.47-3.20)	0.73 (0.26-2.11)	2.91 (1.69-5.04)	1.57 (0.70-3.48)	4.39 (2.82-6.84)
Multivariable HR (95%CI)	1.00	0.86 (0.48-1.52)	2.80 (1.81-4.34)	1.21 (0.46-3.17)	0.74 (0.26-2.12)	2.94 (1.69-5.11)	1.57 (0.71-3.5)	4.44 (2.82-6.99)
PAF (95%CI)		-	26.4 (17.1-34.6)	-	-	5.4 (2.1-8.7)	-	24.2 (17.7-30.1)
Women, n	3,392	1,205	1,550	1,786	964	1332	365	1513
No. of patient-y	30,922	11,740	13,826	16,809	9945	12,069	3697	13,248
No. of cases	20	19	55	10	12	31	7	54
Age and area-adjusted	1.00	2.09 (1.11-3.93)	3.56 (2.10-6.03)	0.78 (0.36-1.67)	1.69 (0.82-3.51)	2.56 (1.44-4.55)	2.35 (0.98-5.63)	3.45 (2.02-5.90)
Multivariable HR (95%CI)	1.00	2.07 (1.10-3.89)	3.83 (2.25-6.51)	0.80 (0.37-1.73)	1.75 (0.84-3.61)	2.87 (1.60-5.15)	2.49 (1.04-5.96)	4.02 (2.32-6.99)

PAF (95%CI)		4.7 (0.1-9.1)	19.5 (12.0-26.4)	-	-	9.7 (3.9-15.2)	2.0 (0.0-4.5)	19.5 (12.1-26.3)
Age, 65-74 y								
Men, n	349	470	1,151	47	139	606		
No. of patient-y	2,973	3,992	9,033	386	1104	4412		
No. of cases	20	29	122	1	6	60		
Age and area-adjusted HR (95%CI)	1.00	1.19 (0.68-2.11)	1.98 (1.23-3.17)	-	0.89 (0.36-2.22)	2.12 (1.28-3.53)		
Multivariable HR (95%CI)	1.00	1.19 (0.68-2.12)	2.00 (1.24-3.22)	-	0.91 (0.36-2.26)	2.17 (1.30-3.64)		
PAF (95%CI)		-	29.4 (11.5-43.6)	-	-	13.6 (5.2-21.3)		
Women, n	386	324	788	295	441	1690		
No. of patient-y	3,223	2,941	6,810	2,504	3899	14,234		
No. of cases	11	14	56	8	27	134		
Age and area-adjusted HR (95%CI)	1.00	1.38 (0.63-3.05)	1.99 (1.04-3.81)	0.97 (0.39-2.43)	2.06 (1.02-4.15)	2.60 (1.41-4.82)		
Multivariable HR (95%CI)	1.00	1.38 (0.63-3.05)	2.00 (1.04-3.83)	0.97 (0.39-2.43)	2.07 (1.02-4.17)	2.63 (1.41-4.88)		
PAF (95%CI)		-	11.2 (2.0-19.6)	-	5.6 (0.4-10.5)	33.2 (16.9-46.3)		

*Waist cutoff values using 90cm for men and 80cm for women. Multivariable hazard ratio (HR): adjusted further for non-high-density lipoprotein (HDL) cholesterol.
Referral risk levels were defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or medication use; triglycerides level ≥3.39mmol/L (300mg/dL) and/or HDL-cholesterol level ≤0.91mmol/L (34mg/dL) or non-HDL-cholesterol level ≥4.40mmol/L (170mg/dL) or medication use; fasting glucose level ≥7.0 mmol/L (126 mg/dL) or non-fasting glucose level ≥1.11mmol/L (200mg/dL) or medication use.
Multivariable HR: adjusted further for non-HDL cholesterol. For ages of 65-74 years, the ISI was collapsed into MSI.