Physical Activity and Risk of Metabolic Phenotypes of Obesity: A Prospective Taiwanese Cohort Study in More Than Two Hundred Thousand Adults

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ABSTRACT

Objective: To examine the association between physical activity (PA) and the risk of metabolically unhealthy obesity (MUO) or metabolically healthy obesity (MHO) in Asian adults. **Patients and Methods**: Data were taken from 205,745 healthy individuals aged ≥18 years. Individuals were classified as inactive, lower or upper insufficiently active, active, and high active. Metabolically unhealthy was defined as having ≥1 of the metabolic syndrome criteria, excluding the abdominal obesity criterion. **Results**: The percentage of metabolically healthy normal-weight (MHNW), metabolically healthy overweight (MHOW), MHO and MUO in our cohort was 30.8%, 5.8%, 4.1% and 20.7%, respectively. During a mean follow-up of 6 years (range, 0.5-19 years), among MHNW participants, 1890 (3.0%) and 1174 (1.9%) developed MUO and MHO, respectively. Among MHOW participants, 3404 (28.4%) developed MUO and 2734 (22.8%) MHO. A total of 5506 (66.1%) participants moved from MHO to MUO, and 5675 (13.3%) moved from MUO to MHO. Compared with being inactive, MHNW individuals who were active or high active showed lower risk of MUO. Among those with MHOW, being high active was associated with reduced risk of MUO and MHO. Although among MHO participants PA was not associated with incident MUO, being active or high active was linked to a greater likelihood of moving from MUO to MHO. **Conclusion:** PA may prevent the development of both MHO and MUO. PA also helps to increase the transition from MUO to MHO, which may contribute to reduce subsequent development of type 2 diabetes mellitus and major CVD complications.

INTRODUCTION

Obesity currently affects more than 600 million adults worldwide, and is predicted to affect more than one billion people by 2030 (1,2). This pandemic is a major public health problem because obesity is associated with numerous health consequences, including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), cancer, and musculoskeletal disorders (3,4). Also of interest is that obesity is associated with metabolic complications, such as hypertension, dyslipidemia, and insulin resistance (5-6). The detrimental metabolic effect of obesity is widely known at population level, but substantial heterogeneity exists in individual responses to obesity (5).

Among the individuals with obesity, those with an unfavorable metabolic profile have a substantially increased risk of CVD, cancer, and premature death (5-7); this phenotype has been referred to as 'metabolically unhealthy obesity' (MUO). Also, there are people with obesity who do not present elevated metabolic risk factors; this phenotype is named 'metabolically healthy obesity' (MHO), and entails a lower risk of T2DM and CVD complications than MUO (5-7). In the current MUO and MHO scenario, there is compelling evidence on their characterization and prognosis but little is known about prevention and management (5-7).

Some studies have shown that performing higher levels of physical activity (PA) may prevent obesity (8-12), but they have not typically considered the two metabolic obesity phenotypes. Also, the role of PA to protect the transition from MHO to MUO is poorly understood (13,14). Of particular interest for obesity management would be to understand whether PA could help to move patients from a state of MUO to MHO (15). Thus, we aimed to examine the role of PA in the development of MUO and MHO among adults without obesity (i.e. obesity prevention) and with obesity (i.e. obesity management) from a large prospective cohort in Taiwan.

METHODS

Study cohort and design

The present study used data from the MJ Cohort (16), which is a prospective study of women and men who participated in a standardized medical screening program operated by the MJ Health Management Institution in Taiwan. Participants completed a self-administered questionnaire, underwent a physical examination, and provided biological samples for laboratory tests, which conformed to ISO9001 for quality management. The MJ Cohort has enrolled more than 650,000 participants nationwide since 01/01/1994, and they were mostly young and middle-aged adults but some of their offspring, parents, or relatives in other age strata also completed the medical screening and were included in the cohort. Participants were encouraged to return annually and data have been updated every year during follow-up visits to the MJ Health Management Institution.

For the present study, we initially selected women and men aged ≥18 years with baseline health data collected during 01/01/1997-12/31/2013. The inclusion criteria were: 1) being free of cancer or CVD at baseline; 2) having at least one follow-up visit through 12/31/2016; and 3) complete data at baseline on PA and other study variables. A total of 102,632 women and 103,113 men (n= 205,745) met these criteria in the MJ Health database.

Study participants provided informed written consent to participate for processing the data from their medical screening, and the study protocols were approved by the Institutional Review Boards of the MJ Health Management Institution and the National Health Research Institutes in Taiwan. To prevent research errors caused by the quality of the data, the MJ Health Resource Center conducted data cleaning (e.g. inaccurate or extreme values) (17). Data on individual identification were removed and remained anonymous in the database during the entire study process (18).

Study variables

Participants completed a health and lifestyle questionnaire at baseline, asking about sex, age, educational attainment, marital status, smoking, alcohol consumption and PA (16). Leisure-time PA was assessed by the validated MJ PA Questionnaire (19,20). Participants were asked to report the intensity, frequency, and duration of PA in the last month, with several examples of activity types given for four intensity categories: light (e.g. slow walking), moderate (e.g. brisk walking), medium-vigorous (e.g. jogging), or high-vigorous (e.g. running). A metabolic equivalent (MET; 3.5 ml/kg/min or 1 kcal/kg/h) value of 2.5 was assigned for light, 4.5 for moderate, 6.5 for medium-vigorous, and 8.5 for high-vigorous PA intensities according to the Compendium of Physical Activities (21). To calculate the total volume of PA, the MET value for a given intensity was multiplied by the frequency and duration, resulting in total MET-h/week of PA. Study participants were classified into five PA volumes: 'inactive' (0 MET-h/week), 'lower insufficiently active' (0.01–3.74 MET-h/week [equivalent to 0.01–74 min/week in moderate-intensity PA]), 'upper insufficiently active' (3.75–7.49 MET-h/week [equivalent to 75–149 min/week in moderate-intensity PA]), and 'active' (7.50–15.00 MET-h/week [equivalent to 150–300 min/week in moderate-intensity PA]) and 'high active' (>15.00 MET-h/week [equivalent to >300 min/week in moderate-intensity PA]). This classification conforms to current PA guidelines, with active participants meeting the recommended amount of PA for substantial health benefits (22).

At baseline and follow-up visits, physical examinations were performed and overnight fasting blood samples were collected and analyzed using standard analytical procedures, as reported elsewhere (23). Body weight to the nearest 0.1 kg and height to the nearest mm were measured using an automatic device (Nakamura KN-5000A, Tokyo, Japan). Body mass index (BMI) was calculated as weight in kg divided by squared height in m; the Asian-specific cut-off points of 23 and 25 kg/m^2 were employed to identify overweight and obesity, respectively, in the cohort (24). Blood pressure (BP) in the left arm was measured twice at 10-min interval,

with the participants seated after a 5-min rest, using a computerized auto-mercury sphygmomanometer (Citizen CH-5000, Tokyo, Japan) by well trained nurses; the mean of the 2 measurements was used for the analysis. Serum glucose, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) were analyzed using the Hitachi 7150 auto-analyzer (Hitachi Ltd., Tokyo, Japan). As suggested in a recent proposal to harmonize the metabolic phenotypes of obesity (6), participants were classified as being metabolically unhealthy if they met ≥1 of the following metabolic syndrome criteria (25): 1) systolic BP (SBP) ≥130 mmHg or on anti-hypertensive medication; 2) TGs ≥150 mg/dL; 3) HDL-C <40 mg/dL in men or <50 mg/dL in women; and 4) fasting glucose ≥100 mg/dL or on anti-diabetic medication.

Statistical analysis

Baseline characteristics of the total sample were summarized as mean and standard deviation (SD) for continuous variables, and as percentage for categorical variables. Differences across the 5 PA categories were examined using analysis of variance for continuous variables and χ^2 tests for categorical variables.

According to the aims of the present study, we initially restricted the analyses on four groups of participants with the following metabolic phenotypes at baseline: metabolically healthy normal weight (MHNW) individuals, metabolically healthy overweight (MHOW) individuals, and the two obesity phenotypes. Differences in baseline PA levels among the four study groups were examined by one-way analysis of covariance, after adjustment for age, sex, year of baseline examination, educational attainment, marital status, smoking, meal patterns and alcohol consumption.

Follow-up time was computed as the difference between the date of the baseline health screening and the date of the visit where MUO or MHO was first reported or the last visit through the end of 12/31/2016. To examine the dose-response relationship between PA as a

continuous variable and the incidence of MUO or MHO by study group, we used restricted cubic spline Cox regressions, with knots at the 10^{th}, 50^{th}, and 90^{th} percentile. PA (MET-h/week) was truncated at the 99th percentile to minimize the influence of outliers. Cox proportional hazards regression analysis was also used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the incidence of MUO or MHO, with PA in categories and the inactive group as reference. Three Cox models were fitted with sequential adjustment for number of variables: model 1 adjusted for age (years), sex (men, women) and year of baseline examination (1997-2013); model 2 additionally adjusted for educational attainment (middle school or below, high school, junior school, college or above), marital status (single, married, widowed), smoking (never, former, current), alcohol drinking (never, former, currently) and meal pattern (suboptimal, optimal); and model 3 additionally adjusted for the baseline values of BMI and the metabolic condition. including fasting glucose, SBP, HDL-C, and TGs. We tested for interactions by sex and age (P>.1), but as none reached statistical significance we present analysis in the total sample.

For clinical purposes, we additionally examined whether PA is associated with conversion from metabolically unhealthy normal weight (MUNW) to MHNW. Similarly, we examined the role of PA in the conversion from metabolically unhealthy overweight to MHOW.

The proportional hazards assumption was checked by comparing the log–log survival plots. Statistical significance was set at 2-sided P<.05. Analyses were performed with STATA v.14. This work adheres to the Strengthening the Reporting of Observational Studies in Epidemiology standards for reporting of observational studies (STROBE).

RESULTS

At baseline, study participants had a mean±SD age of 38.5±12.1 years (range, 18 to 97 years), 50% were women, 61.6% reported junior school or university studies, 64.8% were married, and most of them were never-smokers (73.2%) and never-drinkers (82.4%). As compared with inactive participants (Table 1), participants in the highest categories of self-reported PA, were older, and less frequently women and never-drinkers, with higher BMI and higher levels of cardiometabolic risk factors. The percentage of MHNW, MHOW, MHO and MUO in our cohort was 30.8%, 5.8%, 4.1% and 20.7%, respectively.

Figure 1 shows that those with MHO had higher PA levels than did two of the other three study groups, and differences were particularly large when compared to MUO participants (+0.94 MET-h/week, 95%CI, -0.63 to -1.26). There were also differences between normal weight and overweight participants, but both groups engaged in higher levels of PA than MUO participants (both $P<.001$).

During a mean follow-up of 6 years (range, 0.5 to 19 years), among MHNW participants, 1890 (3.0%) and 1174 (1.9%) developed MUO and MHO, respectively. Among MHOW participants, 3404 (28.4%) developed MUO and 2734 (22.8%) MHO. In the transition between metabolic obesity phenotypes, a total of 5506 (66.1%) participants moved from MHO to MUO, and 5675 (13.3%) participants moved from MUO to MHO.

Figure 2 illustrates the dose-response associations between PA levels and the incidence of MUO and MHO by study group. PA was inversely associated with the risk of MUO in the two non-obese study groups (both *P* for non-linear trend <.01) but not among MHO (*P* for non-linear trend =.07). PA also showed a non-linear inverse association with the incidence of MHO in MHNW and MHOW groups (*P* for non-linear trends .05 and .033, respectively). Importantly, PA was positively associated with the transition to MHO among individuals with MUO (*P* for non-linear trend <.001).

In the MHNW and MHOW groups, being high active was inversely associated with the risk of MUO (HR 0.81, 95%CI: 0.70-0.95, and 0.86, 95%CI: 0.77-0.96, respectively). Also in the normal weight group, being active was associated with a reduction in MUO incidence (HR 0.72, 95%CI: 0.60-0.87) (Table 2). Being active or high active was not associated with a lower risk of moving from MHO to MUO (Table 2).

Among those with MHNW, being upper insufficiently active or active was associated with lower risk of MHO (HR 0.81, 95%CI: 0.69-0.94 and HR 0.74, 95%CI: 0.58-0.93, respectively). Among those with MHOW, being upper insufficiently active or high active was associated with lower risk of MHO (HR 0.86, 95%CI: 0.77-0.95 and HR 0.88, 95%CI: 0.79-0.99, respectively). Moreover, being active or high active was linked to a greater likelihood of moving from MUO to MHO (HR 1.13**,** 95%CI: 1.03-1.23 and 1.17**,** 95%CI: 1.08-1.28, respectively) (Table 3).

Since over half of the participants in the MHOW group developed any obesity, we also examined the associations of PA with progression to both overweight phenotypes; this analysis also showed that PA was inversely associated with incidence of MUOW or MHOW, even though the strength of the association was stronger for MUOW prevention (Supplementary Figure 1 and Table 1). Additional analyses by examining the associations of PA with conversion from MUNW to MHNW or MUOW to MHOW showed a clear null association (Supplementary Figure 2 and Table 2).

DISCUSSION

In this study conducted in a large cohort in Taiwan, we obtained two main novel findings. First, PA was inversely associated with the incidence of MUO and MHO; this supports clinical and public health strategies based on PA promotion because they might prevent obesity, irrespective of the type of metabolic phenotype (26,27). And second, higher PA increased the likelihood of transition from MUO to MHO, which suggests that PA could be a key intervention for obesity management because it might delay the occurrence of T2DM and major adverse CVD outcomes associated with obesity.

There is strong evidence that PA contributes to weight loss and its maintenance in randomized clinical trials and prospective cohorts (8,9,28); some potential mechanisms are the reduction of fat mass, gain of lean mass, increase of energy expenditure, and the maintenance or even increase of the resting metabolic rate (29). Although this might entail that PA can reduce the risk of obesity, only a few studies have examined this issue. Among 288,498 men and women from the EPIC cohort followed for 5.1 years, the odds of becoming obese were reduced by 7% in men and 10% in women for a one-category difference in the Cambridge PA index (10). Also in 23,108 individuals, aged 18-84 years, in the Stockholm Public Health Cohort 2002 followed until 2010, those who engaged in regular PA vs. inactive individuals had a lower obesity risk (relative risk 0.58, 95%CI: 0.42-0.81 and relative risk 0.37, 95%CI: 0.25-0.54, in men and women, respectively) (11). Moreover, in 20,259 African-American women aged <40 years, vigorous PA but not brisk walking was associated with lower incidence of obesity (12). These previous studies, however, did not assess the obesity phenotypes.

Our results extend previous evidence by showing that PA may prevent obesity irrespective of the metabolic phenotype. However, the associations of PA were stronger for the development of MUO than MHO. This is important for preventive purposes because

MUO individuals show higher risk for premature death, CVD and T2DM than those with MHO and because MUO is more prevalent than MHO. Also of note is that the study associations were more clearly observed in people with overweight than with normal weight, because in the former even moderate PA (i.e. half of the recommended PA) was linked to lower risk of MUO and MHO; this finding is in agreement with evidence from clinical trials (8,28). Given that about 28% of overweight participants developed MUO (vs. 1.9% who developed MHO), clinical and public health strategies promoting PA that target the numerous overweight people may be crucial to prevent control MUO at the population level.

The reason why some people with obesity do not show cardiometabolic abnormalities are not well known, but some biological mechanisms have been suggested: genetic susceptibility, levels of physical fitness, intergenerational and early risk factors, distribution of adiposity and maternal and environmental factors (5-7,30,31). Moreover, there is recent evidence that MHO is a rare, intermediate, and unstable condition (32-37). In our study, as in a recent systematic review (38), people with MHO had notably higher levels of PA than those with MUO, but it did not prevent that more than two thirds of the former transitioned to the MUO phenotype. Thus, other health behaviors and biological risk factors should be studied to identify strategies aimed to delay the metabolic complications in people with obesity (7,26).

The transition from MUO to MHO has been poorly studied (14). Although only 13% of participants with MUO moved to MHO, meeting the recommended amount of PA was associated with a 15% higher likelihood of transitioning into MHO. This analysis was adjusted for baseline body weight, which emphasize the importance of PA to protect from metabolic complications across the levels of obesity, independent of effects on bodyweight. Given the difficulty in losing weight, conversion to MHO among those with MUO is an important health outcome (14); unfortunately, individuals with MUO at baseline showed the lowest levels of PA, so becoming physically active could be particularly challenging for this

group of patients (38). Hence, strategies to increase PA levels in people with MUO are warranted, and it is likely that any PA may be better than no PA (26,27,39).

Some strengths of this study are the large sample size and the long follow-up, including yearly health screenings to identify the onset of each outcome variable. Another strength is the use of objective measurements of obesity and metabolic risk factors, which have been assessed by standardized clinical examinations and laboratory tests. This study also has its limitations. First, PA was self-reported at, which usually overestimates the amount of PA and, thus, underestimates its association with health outcomes. Also, PA information was obtained at baseline and although our analyses assume that PA levels have certain stability over time, some changes are still possible and would likely have led to an underestimation of the protective impact of PA on obesity. Second, study participants may not be representing the general population of Taiwan, because they had somewhat higher socioeconomic status (15); however, the prevalence of CVD risk factors and the incidence and mortality of CVD and cancer in this cohort are comparable to those in the general Taiwanese population (15). Notwithstanding this, our results should be confirmed in other Asian and non-Asian populations, who may have particularly high prevalence of obesity and severe obesity, we lacked information on obesity history, thus we could not distinguish those individuals with long-time obesity from those who recently gained enough weight or fat mass to become obese at baseline; duration of obesity is tightly related to metabolic dysfunction possible regardless of PA (37); however, this did not preclude to observe a clear protective association between PA and MUO. Additionally, although analyses were adjusted for several socio-demographic and lifestyle factors, we had no information on other potentially important variables (e.g. family history, diet quality) and certain residual confounding may persist. Finally, we based obesity on BMI and using the lower cut-points used in Asian populations; despite the

limitations of BMI in isolated individuals, BMI is very accurate to predict risk for adult populations (6,40).

CONCLUSION

Our results have important practical implications. For public health purposes, these results suggest that higher levels of PA may help to prevent obesity, regardless of being metabolically healthy or not; importantly, PA showed a greater beneficial association with MUO, which is the most harmful and prevalent phenotype. As regards to obesity management, our results also suggest that PA may increase the likelihood of transition from MUO to MHO and, thus, reduce the risk of some adverse health consequences of obesity, including potentially T2DM, CVD, and all-cause and CVD-mortality.

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Table 1. Baseline characteristics of the 205,745 cohort participants, by physical activity categories

	Inactive (0 MET-h/week)	**Lower insufficiently active** (0.01–3.74 MET-h/week)	**Upper insufficiently active** (3.75–7.49 MET-h/week)	**Active** (7.50–15.00 MET-h/week)	**Highly active** (>15.00 MET-h/week)
n	60230	48032	46089	24922	26472
Female, %	55.9	56.3	48.1	45.5	31.94
Age, y	36.9±11.0	37.1±11.0	37.3±11.4	43.5±13.7	42.1±13.9
Educational attainment, %					
Middle school or below	17.3	15.1	12.2	23.5	20.2
High school	24.5	20.6	19.4	20.2	19.7
Junior school	25.8	23.6	24.3	20.2	19.8
College or above	32.4	40.7	44.1	36.1	40.3
Marital status, %					
Single	31.3	34.7	35.0	25.2	31.3
Married	66.3	62.9	62.5	69.5	64.8
Widowed	2.4	2.4	2.5	5.3	3.9
Smoking status, %					
Never	73.2	73.2	74.8	73.3	70.4
Former	5.2	5.0	5.7	7.1	8.7
Currently	21.6	21.8	19.5	19.6	20.9
Alcohol drinking, %					
Never	84.7	83.6	83.2	79.0	76.6
Former	2.2	2.3	2.0	2.7	3.1
Currently	13.1	14.1	14.8	18.3	20.3
Optimal meal pattern, %	52.6	53.7	62.4	67.1	67.5
Body mass index, kg/m^2	22.5±3.6	22.7±3.7	22.8±3.5	23.3±3.3	23.4±3.2
Systolic blood pressure, mm Hg	116.1±16.8	116.2±16.6	117.6±16.7	121.6±18.5	122.2±17.6
Antihypertensive drugs, %	2.8	3.2	3.5	6.9	6.2
Fasting glucose, mg/dL	96.6±18.5	97.2±18.7	97.1±17.8	99.7±21.5	99.3±19.7
Antidiabetic drugs, %	1.0	1.5	1.4	2.6	2.3
HDL-cholesterol, mg/dL	53.0±14.8	54.6±14.7	53.0±14.5	52.8±14.6	53.1±14.4
Triglycerides, mg/dL	111.8±94.5	110.5±92.9	111.4±87.4	119.2±94.8	114.5±89.6

Data are presented as mean ± SD or %. All differences across physical activity categories were $P<.001$

Table 2. Hazard ratios (95% confidence interval) of incident metabolically unhealthy obesity (MUO) according to physical activity categories, by study groups

	Inactive (0 MET-h/week)	**Lower insufficiently active** (0.01–3.74 MET-h/week)	**Upper insufficiently active** (3.75–7.49 MET-h/week)	**Active** (7.50–15.00 MET-h/week)	**Highly active** (>15.00 MET-h/week)
Metabolically healthy normal weight					
N	20219	16509	14523	5920	6237
Cases	648	384	467	148	243
Model 1 HR (95%CI)	1 (Reference)	0.96 (0.84-1.10)	1.01 (0.90-1.14)	**0.82 (0.68-0.98)**	1.01 (0.87-1.18)
Model 2 HR (95%CI)	1 (Reference)	0.96 (0.84-1.09)	1.05 (0.93-1.19)	0.84 (0.70-1.01)	1.02 (0.88-1.19)
Model 3 HR (95%CI)	1 (Reference)	0.96 (0.84-1.10)	0.93 (0.83-1.05)	**0.72 (0.60-0.87)**	**0.81 (0.70-0.95)**
Metabolically healthy overweight					
N	3098	2719	2854	1445	1886
Cases	935	766	805	383	515
Model 1 HR (95%CI)	1 (Reference)	1.07 (0.97-1.18)	**0.90 (0.82-0.99)**	0.92 (0.81-1.03)	**0.82 (0.73-0.91)**
Model 2 HR (95%CI)	1 (Reference)	1.07 (0.97-1.18)	0.91 (0.83-1.01)	0.92 (0.81-1.04)	**0.83 (0.74-0.92)**
Model 3 HR (95%CI)	1 (Reference)	1.08 (0.98-1.20)	0.91 (0.82-1.01)	0.94 (0.84-1.07)	**0.86 (0.77-0.96)**
Metabolically healthy obesity					
N	2209	2006	1821	978	1315
Cases	1486	1316	1193	623	888
Model 1 HR (95%CI)	1 (Reference)	1.01 (0.94-1.09)	0.98 (0.91-1.06)	0.92 (0.83-1.01)	**0.89 (0.82-0.97)**
Model 2 HR (95%CI)	1 (Reference)	1.01 (0.94-1.09)	0.99 (0.91-1.07)	0.93 (0.84-1.02)	**0.90 (0.82-0.98)**
Model 3 HR (95%CI)	1 (Reference)	1.01 (0.94-1.09)	1.00 (0.93-1.08)	0.95 (0.86-1.04)	0.93 (0.85-1.02)

HR: Hazard ratio; CI: Confidence intervals. Model 1 adjusted for age, sex and year of baseline examination. Model 2 adjusted as model 1 and additionally for educational attainment, marital status, smoking, alcohol drinking and meal pattern. Model 3 adjusted as model 2 and additionally for the baseline values of body mass index, fasting glucose, systolic blood pressure, HDL-c, and triglycerides.

Table 3. Hazard ratios (95% confidence interval) of incident metabolically healthy obesity (MHO) according to physical activity categories, by study groups

	Inactive (0 MET-h/week)	**Lower insufficiently active** (0.01–3.74 MET-h/week)	**Upper insufficiently active** (3.75–7.49 MET-h/week)	**Active** (7.50–15.00 MET-h/week)	**Highly active** (>15.00 MET-h/week)
Metabolically healthy normal weight					
N	20219	16509	14523	5920	6237
Cases	419	234	275	90	156
Model 1 HR (95%CI)	1 (Reference)	0.87 (0.74-1.03)	0.94 (0.81-1.10)	0.87 (0.69-1.09)	1.18 (0.98-1.43)
Model 2 HR (95%CI)	1 (Reference)	0.87 (0.73-1.03)	0.96 (0.82-1.12)	0.88 (0.70-1.11)	1.19 (0.98-1.44)
Model 3 HR (95%CI)	1 (Reference)	0.87 (0.74-1.03)	**0.81 (0.69-0.94)**	**0.74 (0.58-0.93)**	0.85 (0.70-1.03)
Metabolically healthy overweight					
N	3098	2719	2854	1445	1886
Cases	757	603	628	308	438
Model 1 HR (95%CI)	1 (Reference)	0.95 (0.85-1.06)	**0.87 (0.79-0.97)**	0.98 (0.86-1.12)	0.95 (0.85-1.07)
Model 2 HR (95%CI)	1 (Reference)	0.95 (0.85-1.07)	**0.87 (0.78-0.97)**	0.97 (0.85-1.11)	0.94 (0.83-1.06)
Model 3 HR (95%CI)	1 (Reference)	0.99 (0.88-1.10)	**0.86 (0.77-0.95)**	0.95 (0.83-1.09)	**0.88 (0.77-0.99)**
Metabolically unhealthy obesity					
N	11497	9726	9112	6083	6148
Cases	1507	1254	1246	772	896
Model 1 HR (95%CI)	1 (Reference)	1.06 (0.98-1.14)	1.07 (0.99-1.16)	**1.24 (1.14-1.36)**	**1.36 (1.25-1.47)**
Model 2 HR (95%CI)	1 (Reference)	1.06 (0.98-1.15)	1.05 (0.97-1.13)	**1.22 (1.12-1.34)**	**1.33 (1.22-1.45)**
Model 3 HR (95%CI)	1 (Reference)	1.05 (0.97-1.13)	1.03 (0.96-1.11)	**1.13 (1.03-1.23)**	**1.17 (1.08-1.28)**

HR: Hazard ratio; CI: Confidence intervals. Model 1 adjusted for age, sex and year of baseline examination. Model 2 adjusted as model 1 and additionally for educational attainment, marital status, smoking, alcohol drinking and meal pattern. Model 3 adjusted as model 2 and additionally for the baseline values of body mass index, fasting glucose, systolic blood pressure, HDL-c, and triglycerides.

FIGURE LEGENDS

Figure 1. Levels of physical activity by study groups. The circled points and error bars represent adjusted means and 95% confidence intervals, respectively. Analyses were adjusted for age, sex, year of baseline examination, educational attainment, marital status, smoking, meal pattern, and alcohol drinking.

Figure 2. Incidence of metabolically unhealthy obesity (MUO) and metabolically healthy obesity (MHO) according to physical activity levels by study groups. Solid lines indicate hazard ratios and dashed lines indicate 95% confidence intervals. Analyses were adjusted for age, sex, year of baseline examination, educational attainment, marital status, smoking, alcohol drinking, meal pattern, and baseline values of body mass index, fasting glucose, systolic blood pressure, HDL-c, and triglycerides.