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ORIGINAL RESEARCH

Association Between Moderate-to-Vigorous Physical Activity and the Risk of Major Adverse Cardiovascular Events or Mortality in People With Various Metabolic Syndrome Status: A Nationwide Population-Based Cohort Study Including 6 Million People

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BACKGROUND: A population-scale evidence for the association between moderate-to-vigorous physical activity (MV-PA) and risks of major adverse cardiovascular event (MACE) or all-cause mortality in people with various metabolic syndrome (MetS) status is warranted.

METHODS AND RESULTS: We performed a nationwide retrospective cohort study based on the claims database of South Korea. We included people who received ≥3 national health screenings from 2009 to 2013 without a previous MACE history. We determined the MetS status of 6 108 077 people: MetS-chronic (N=864 063), MetS-developed (N=348 163), MetS-recovery (N=348 313), and MetS-free (N=4 547 538). The exposure was self-reported MV-PA frequencies. The outcome was incident MACEs or all-cause mortality. The incidence rate ratios (IRR) were calculated with adjustments for clinical/demographic characteristics. During the median follow-up of 4.28 years, 78 770 and 51 840 people experienced MACEs or died, respectively. Those who engaged in MV-PA had a significantly lower risk of MACEs or all-cause mortality than those not engaged in MV-PA in every spectrum of MetS. Even among those who were free from MetS (for MACEs, IRR 0.94 [0.92–0.97], for all-cause mortality, IRR 0.85 [0.82–0.87]) or who had already recovered from MetS (for MACEs, IRR 0.89 [0.84–0.95], for all-cause mortality, IRR 0.74 [0.68–0.81]), 1 to 2 days per week of MV-PA were significantly associated with lower risk of the adverse outcomes when compared with not being engaged in MV-PA. Those who were engaged in MV-PA more frequently also had significantly lower risks of MACEs or all-cause mortality.

CONCLUSIONS: This nationwide study suggests that MV-PA may be recommended to the general population regardless of recent MetS status.

Key Words: cardiovascular outcomes ■ epidemiology ■ metabolic syndrome ■ mortality ■ physical exercise

Physical activity reduces the risk of major adverse cardiovascular events (MACEs) and is associated with a lower risk of death from all causes.[1–4] On the other hand, the presence of metabolic risk factors, including central obesity, elevated blood pressure, dyslipidemia, and impaired glucose tolerance, is

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CLINICAL PERSPECTIVE

What Is New?

- Regardless of the recent status of metabolic syndrome, individuals engaged in moderate-to-vigorous physical activity had lower risk for major adverse cardiovascular events and all-cause mortality in a large nationwide cohort in South Korea.
- Even those who were free from metabolic syndrome or who did not improve in their metabolic profiles showed lower risk for major adverse cardiovascular events and all-cause mortality when individuals were engaged in any degree of moderate-to-vigorous physical activity.

What Are the Clinical Implications?

- Healthcare providers should emphasize the importance of moderate-to-vigorous physical activity for people even if they are free from metabolic syndrome or have already recovered from metabolic syndrome.
- In those with worsening metabolic health or no obvious improvements in metabolic health, moderate-to-vigorous physical activity may still be recommended, as certain benefits of moderate-to-vigorous physical activity may be independent of the status of measurable metabolic parameters.

Nonstandard Abbreviations and Acronyms

MetS	metabolic syndrome
MV-PA	moderate-to-vigorous physical activity

related to higher MACE risks, and the cluster of such components has been known as metabolic syndrome (MetS).[5,6] Considering the significant impact of MetS on cardiovascular health, a substantial amount of medical resources have been invested in promoting physical activity and controlling metabolic risk factors.

Moderate-to-vigorous physical activity (MV-PA), commonly referred to as activities with an intensity equivalent or stronger than that of light bicycling or brisk walking, is considered the main type of activity that leads to a lower MACE or mortality risk.[7,8] The role of MV-PA in improving MetS profiles has been understood to be the major mechanism underlying its beneficial effect on cardiovascular health.[9] However, there were relatively rare large-scale evidences regarding whether MV-PA should be promoted to those free from MetS or those lacking improvement in MetS parameters.[2,10] In addition, although a dynamic MetS status is prominently associated with an altered MACE risk,[11] a population-based study showing whether the benefits of MV-PA are present along the spectrum of MetS has yet to be reported. Such evidence is essential because if the clinical benefits of MV-PA are present regardless of the presence or severity of MetS, the necessity of encouraging MV-PA among people with diverse MetS status could be elucidated.[2,12] Furthermore, given that mechanisms beyond controlling the traditional risk factors have been emphasized with regard to the benefits of physical activity,[13,14] clinical evidence showing whether the benefits of MV-PA exist independent from MetS status is needed.

In this nationwide cohort study, we investigated the association between self-reported MV-PA and the risk of MACEs and all-cause mortality; the study included ≈6 million people who had different MetS states during a serial course of national health screenings in South Korea. We hypothesized that the benefits of MV-PA with regard to lower risk of MACEs or all-cause mortality would be present independent from recent status of MetS or baseline MetS severity.

METHODS

Ethical Approval

The institutional review board of Seoul National University Hospital (no. E-1806-112-951) approved the study. The institutional review board waived the need for informed consent as we obtained anonymous data from the National Health Insurance Service of Korea after obtaining approval (no. NHIS-2018-1-247). The study was conducted in accordance with the Declaration of Helsinki.

Data Sources

The data sets analyzed during the current study are available in the National Health Insurance Sharing Service of Korea (URL: https://nhiss.nhis.or.kr/bd/ab/bdaya001iv.do, last accessed January 14, 2020) after acquiring approval from the organization.

Study Design and Setting

The study was a retrospective nationwide cohort study. The study environment has been described in our previous studies.[11,15] South Korea provides a nationwide health insurance service for all Korean people.[16] A free-of-charge national health screening is provided for insurance subscribers in Korea, including an evaluation for MetS, a cancer screening, a lifestyle assessment, and other clinical investigations. From the National Health Insurance Database,[17] we used the health screening data and

claims information to identify the study populations' dynamic MetS status and the questionnaire results to determine the frequency of MV-PA. The MACE outcome was identifiable within the claims database through diagnostic codes, history of admission, and intervention histories. The death outcome was collected from the death registries.

Study Population

A graphical description of the time windows in which the study population was identified, covariates or exposure variables were collected, and outcomes during follow-up were identified is shown in Figure S1.[18] The study population criteria and definitions of the study groups were similar as those implemented in our previous study.[11] We identified adults (≥20 years old) who received ≥3 national health screenings from 2009 to 2013 in Korea. The first 3 health screenings (S1, S2, and S3) were the inclusion period determining the study population.

We first excluded those who had missing information in variables needed to determine their MetS status, baseline laboratory results used as covariates, and baseline questionnaire results. After these individuals were excluded, people with an identifiable MetS status in ≥3 health examinations without missing information for the covariates or exposures remained. Next, we excluded people according to clinical eligibility; those with undetermined MetS status—those who had transient changes in their MetS status, because we aimed to include people with stable changes in or maintenance of their MetS status, or who had changes at S3, as the maintenance of the change for at least 1 health screening during the inclusion period was needed, were excluded. As we intended to study incident MACE risks in people without significant baseline kidney function impairment, we excluded those with prevalent MACEs before the initiation of follow-up (a day after S3) and those with indicators of kidney diseases (baseline estimated glomerular filtration rate <60 mL/min per 1.73 m^2 calculated using the Modification of Diet in Renal Disease equation, a chronic kidney disease diagnostic code, or a history of renal replacement therapy).

Study Groups

MetS status were determined using the harmonizing criteria in each of the first 3 health screening (S1, S2, and S3), and people fulfilling ≥3 of the following 5 MetS components were considered to have MetS in the according health screening[6]: central obesity (waist circumference ≥90 cm for males, ≥80 cm for females among Asians); high triglycerides (≥150 mg/dL) or the use of a relevant drug; low high-density lipoprotein cholesterol levels (<40 mg/dL for males, 50 mg/dL for females) or the use of a relevant drug; high blood pressure (systolic ≥130 and/or diastolic ≥80 mm Hg) or the use of an antihypertensive drug; and impaired glucose tolerance (fasting glucose ≥100 mg/dL) or the use of an antidiabetic medication.

Based on the identified MetS status in the first 3 health screenings (S1, S2, and S3), 4 study groups were defined (Figure 1): the MetS-free group, composed of those who were consistently free from MetS during the inclusion period; the MetS-chronic group, composed of those who had MetS consistently throughout the inclusion period; the MetS-recovery group, composed of those who stably recovered from preexisting MetS (presence of MetS at S1 but not at S2 and S3); and the MetS-developed group, composed of those who newly developed MetS that was consistently identified in subsequent health screenings (absence of MetS at S1 but MetS presence at S2 and S3).

Physical Activity Variables and Other Variables

The third health screening (S3) was the time point when baseline characteristics were collected and follow-up was initiated. The self-reported frequency of MV-PA was collected through a questionnaire asking how many days during a week the individual engaged in physical activity, which was stratified into 3 intensities: vigorous activity was defined as more than 20 minutes of activity that renders one almost out of breath, moderate activity was defined as more than 30 minutes of activity requiring fast breathing, and light activity was more than 30 minutes of walking or light MV-PA per day. The frequency of MV-PA was stratified as none, 1 to 2 days per week, 3 to 4 days per week, and ≥5 days per week. The representative examples of the MV-PAs were provided for the responders and the complete questionnaire used during the general health screening can be found in Figure S2.[19] The questionnaire has been developed and distributed by the National Health Insurance Service of Korea with advisory of expert panels. The details of other collected baseline clinical and demographic data are described in Data S1.

Study Outcomes

The first study outcome was the occurrence of MACEs, which consisted of acute myocardial infarction, coronary revascularization, and acute ischemic stroke. Acute myocardial infarction was defined as an admission with an *International Classification of Diseases Tenth, Revision* (*ICD-10*) diagnostic code of I21 or I22. Coronary revascularization was defined by a cardiovascular revascularization procedure history identified in the

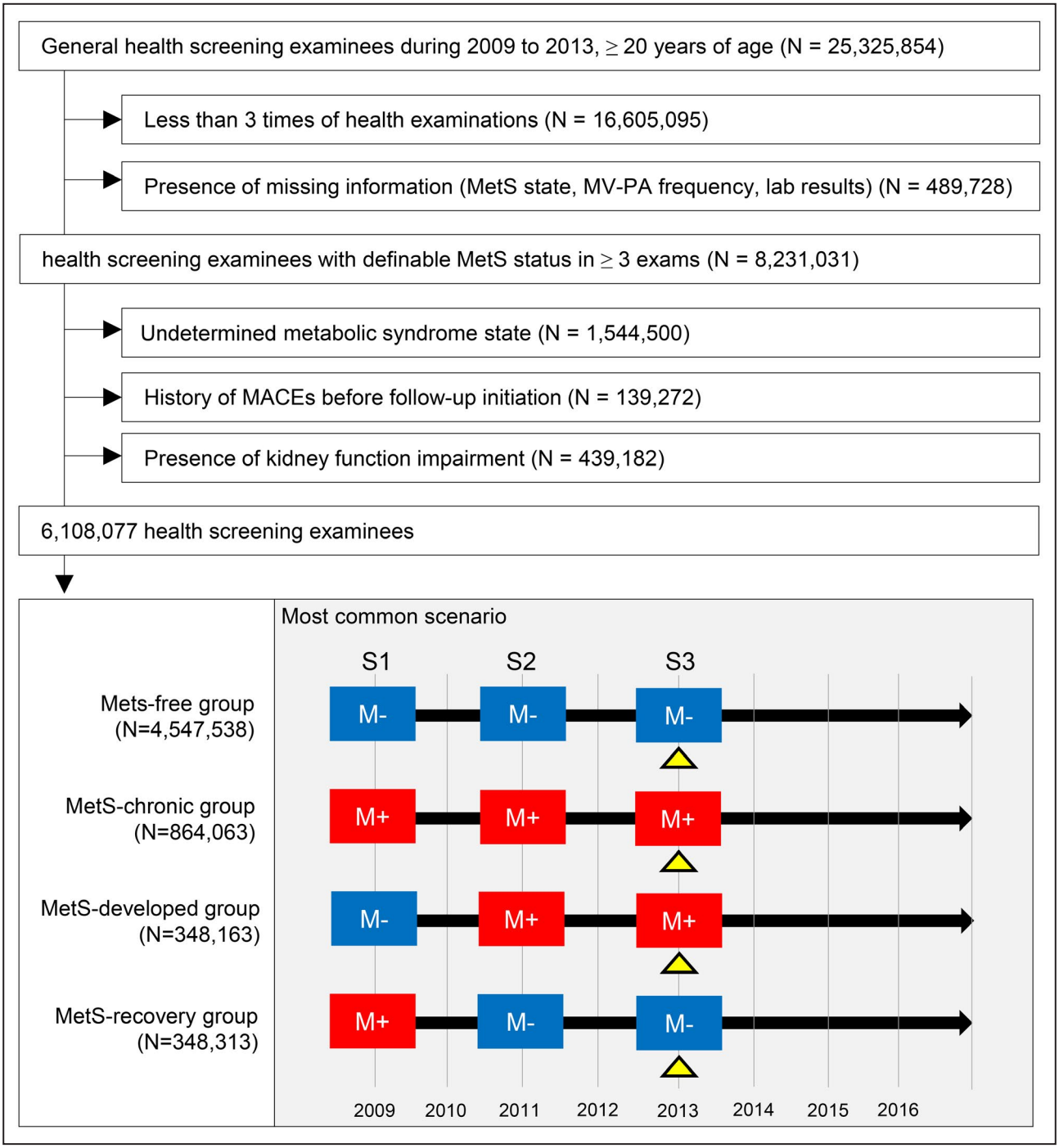

Figure 1. Study population.
The flow diagram for the study population and the common scenario of the study groups. A blue square with "M−" indicates a health screening without the identification of metabolic syndrome. A red square with "M+" indicates a health screening with the identification of metabolic syndrome. The yellow triangles at S3 indicate the baseline time-point at which the baseline clinicodemographic characteristics were collected and follow-up was initiated. MACE indicates major adverse cardiovascular event; MetS, metabolic syndrome; and MV-PA, moderate-to-vigorous physical activity.

claims database. Acute ischemic stroke was defined as an admission with an *ICD-10* diagnostic code of I63.

The second study outcome was all-cause mortality. The death registry information, identifying death dates of all Korean people through death certificates, is available in the claims database and we used the information to define all-cause mortality. Primary causes of death were not available.

The follow-up duration started 1 day after the inclusion period and exposure assessment (1 day after S3), and right-censoring occurred on December 31, 2016, or in death events.

Statistical Analysis

We calculated the incidence rate ratios for MACEs and 95% CIs with Poisson regression. First, we compared all the study subgroups divided according to dynamic MetS status and the frequency of MV-PA, with the MetS-free group with 0 days per week of self-reported MV-PA as the reference group. Second, we assessed the association between the frequency of MV-PA and the risk of MACE or all-cause mortalty in each MetS subgroup, further adjusting for the baseline (S3) severity of MetS within a MetS subgroup. The analysis was repeated in several subgroups, divided according to age (20–39, 40–64, ≥65 years old) or sex (male or female), and those who were initially excluded in the main study population due to their undetermined MetS status. Third, the association of the frequency of MV-PA and MACE risks was assessed in additional subgroups with a consistently absent or present state of individual MetS component. A Kaplan–Meier survival curve was generated with the cumulative incidences. There were no missing values in the data set. Other details regarding the statistical analysis are described in Data S2. All statistical analyses were performed using SAS, and 2-sided $P<0.05$ were considered significant.

RESULTS

Study Population

We screened 25 325 854 adults and identified 8 720 759 people who received ≥3 health screenings during the inclusion period (Figure 1). After exclusion, 8 231 031 people had ≥3 health screenings with identifiable MetS status and self-reported data on MV-PA. After applying the eligibility criteria, we included 6 108 077 people in the final study population. The median follow-up duration was 4.28 (interquartile range 3.50–5.25) years. Among them, 4 547 538 (74.5%) subjects were in the MetS-free group, and 864 063 (14.1%) people were included in the MetS-chronic group. In addition, 348 163 (5.7%) and 348 313 (5.7%) people were included in the MetS-developed and MetS-recovery groups, respectively.

Baseline Characteristics

The MetS-chronic group had the highest median age, worst metabolic parameters, and highest proportion belonging to the low-income population (Table 1). The proportion of those who did not engage in MV-PA was also the highest in the MetS-chronic group and the lowest in the MetS-free group, although the absolute difference between the proportions was small. On the other hand, those who engaged in MV-PA ≥5 days per week were more commonly in the MetS-chronic or MetS-developed group than in those free from MetS at baseline. Regarding the number of MetS components, the MetS-recovery group more frequently had 1 or 2 components of MetS than the MetS-free group. The MetS-chronic group had the largest number of people fulfilling all 5 MetS criteria, and over 60% of the MetS-developed group had 3 MetS components.

MACE and All-Cause Mortality Risks

The numbers of cases and incidence rates for MACEs and all-cause mortality in each subgroup according to MetS status and the frequencies of self-reported MV-PA are shown in Tables 2 and 3. The unadjusted risks showed that the overall risks of MACEs and all-cause mortality were higher in the MetS-developed and MetS-chronic groups than in the MetS-recovery and MetS-free groups. However, within the subgroups, those who did not MV-PA had a higher risk of MACEs or all-cause mortality than those who did (Figure 2, Tables 2 and 3). MV-PA, even when engaged in only 1 to 2 days per week, was associated with a lower risk of MACEs or all-cause mortality when compared with those who were not engaging in MV-PA. Similar trends were identified with regard to the individual MACE outcomes, including acute myocardial infarction, revascularization, and acute ischemic stroke (Tables S1 through S3), but the trend was relatively weak with the revascularization outcome.

MACE and All-Cause Mortality Risks According to the Frequency of MV-PA in Each Dynamic MetS Status Group

In each MetS status subgroup, the association between engaging in MV-PA and a lower risk of MACEs or all-cause mortality was similarly identified (Tables 4 and 5). Even after controlling for MetS severity and smoking and alcohol consumption behaviors, those who engaged in MV-PA had a significantly lower risk of MACEs or all-cause mortality than those who did not engaged in MV-PA in every studied spectrum of MetS. In the fully adjusted model, engaging in MV-PA for 1 to 2 days per week was associated with a 6% to 11% lower risk of MACEs and 9% to 26% for all-cause mortality, respectively, when compared with those who did not engage in MV-PA. Among those who engaged in MV-PA more frequently, the effect sizes were similar or even larger, and engaged in MV-PA ≥5 days per

Table 1. Baseline Characteristics of the Study Patients

Variables	MetS-Free	MetS-Recovery	MetS-Developed	MetS-Chronic
Number of people in each subgroup	4 547 538	348 313	348 163	864 063
Clinical and demographic characteristics at S3				
Age, y	43.8±12.5	50.4±12.7	53.2±12.7	56.7±12.2
Sex (male)	2 608 761 (57.4)	229 853 (66.0)	209 605 (60.2)	480 780 (55.6)
Height, cm	165.4±8.8	165.2±9.3	164.0±9.8	162.9±9.9
Weight, kg	62.3±10.6	67.3±11.5	69.8±12.9	70.7±13.3
Body mass index, kg/m^2	22.7±2.7	24.6±2.8	25.8±3.1	26.5±3.2
Low-income status*	768 815 (16.9)	66 560 (19.1)	69 771 (20.0)	185 068 (21.4)
Place of residence				
Urban	2 026 920 (44.6)	149 289 (42.9)	149 187 (42.9)	376 087 (43.5)
Rural	2 520 618 (55.4)	199 024 (57.1)	198 976 (57.2)	487 976 (56.5)
Charlson Comorbidity Index (score)	0.5±0.9	0.8±1.1	1.1±1.4	1.6±1.7
Hemoglobin, g/dL	14.1±1.6	14.4±1.6	14.4±1.6	14.2±1.6
Aspartate aminotransferase, IU/L	23.7±16.5	26.1±20.9	28.9±21.4	29.4±21.6
Alanine aminotransferase, IU/L	22.1±21.6	26.9±25.2	32.6±27.9	32.9±27.5
Creatinine, mg/dL	0.88±0.19	0.90±0.19	0.89±0.19	0.87±0.19
Estimated glomerular filtration rate, mL/min per 1.73 m^2	93.3±34.5	90.8±33.9	89.2±30.5	88.2±30.0
Self-reported lifestyle, n (%)				
Moderate-to-vigorous activity				
None	2 076 194 (45.7)	162 282 (46.6)	163 527 (47.0)	422 381 (48.9)
1–2 d/wk	1 444 483 (31.8)	105 839 (30.4)	96 746 (27.8)	225 061 (26.1)
3–4 d/wk	650 718 (14.3)	49 482 (14.2)	51 433 (14.8)	125 193 (14.5)
≥5 d/wk	376 143 (8.3)	30 710 (8.8)	36 457 (10.5)	91 428 (10.6)
Smoking				
Nonsmoker	2 704 258 (59.5)	181 422 (52.1)	191 439 (55.0)	502 946 (58.2)
Ex-smoker	604 365 (13.3)	61 512 (17.7)	54 796 (15.7)	143 169 (16.6)
Current light-to-moderate smoker	750 681 (16.5)	54 750 (15.7)	48 995 (14.1)	96 752 (11.2)
Current heavy smoker	488 234 (10.7)	50 629 (14.5)	52 933 (15.2)	121 196 (14.0)
Alcohol				
No alcohol intake	2 098 607 (46.2)	162 816 (46.7)	176 539 (50.7)	479 122 (55.5)
Moderate consumption	347 238 (7.6)	22 231 (6.4)	19 292 (5.5)	42 261 (4.9)
Heavy consumption	2 101 693 (46.2)	163 266 (46.9)	152 332 (43.8)	342 680 (39.7)
Parameters of MetS				
Waist circumference, cm	77.1±8.0	82.5±7.5	86.4±8.0	88.2±8.3
Systolic BP, mm Hg	117.9±12.9	123.8±13.3	129.4±13.6	130.5±14.1
Diastolic BP, mm Hg	74.0±9.0	77.5±9.2	80.5±9.6	80.5±9.8
Glucose, mg/dL	91.6±13.6	97.2±20.3	106.6±25.3	115.3±34.1
Triglycerides, mg/dL	91.59±13.57	97.17±20.26	106.55±25.31	115.3±34.1
High-density lipoprotein cholesterol, mg/dL	105.6±69.3	141.4±96.7	195.8±139.4	205.6±151.7
Baseline N of MetS components, n (%)				
0	1 843 873 (40.6)	37 550 (10.8)	0 (0)	0 (0)
1	1 687 076 (37.1)	120 133 (34.5)	0 (0)	0 (0)
2	1 016 589 (22.4)	190 630 (54.7)	0 (0)	0 (0)
3	0 (0)	0 (0)	209 746 (60.2)	324 261 (37.5)
4	0 (0)	0 (0)	112 611 (32.3)	351 379 (40.7)
5	0 (0)	0 (0)	25 806 (7.4)	188 423 (21.8)

There were no missing values in the table. BP indicates blood pressure; MetS, metabolic syndrome; and S3, screening 3.
*Low income status was determined as the lowest quartile of the nation according to the medical insurance fee.

Table 2. Risks of Major Adverse Cardiovascular Events According to the Frequency of Moderate-to-Vigorous Physical Activity and MetS Status

MetS status	Frequency of MV-PA	Number of People	Number of MACEs	Follow-Up (Person-Years)	Incidence Rate (/1000 Person-Years)	Unadjusted Model		Multivariable Model	
						IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
MetS-free	0 d/wk	1 840 026	17 237	7 981 115	2.16	Reference		Reference	
	1–2 d/wk	1 531 152	8953	6 878 662	1.30	0.60 (0.59–0.62)	<0.001	0.84 (0.82–0.87)	<0.001
	3–4 d/wk	756 270	5226	3 367 586	1.55	0.72 (0.70–0.74)	<0.001	0.80 (0.77–0.82)	<0.001
	≥5 d/wk	420 090	4027	1 825 140	2.21	1.02 (0.99–1.06)	0.222	0.84 (0.81–0.86)	<0.001
MetS-recovery	0 d/wk	145 047	3222	610 909	5.27	2.44 (2.35–2.54)	<0.001	1.40 (1.35–1.46)	<0.001
	1–2 d/wk	104 911	1423	468 051	3.04	1.41 (1.33–1.49)	<0.001	1.24 (1.17–1.31)	<0.001
	3–4 d/wk	59 716	910	262 636	3.46	1.60 (1.50–1.71)	<0.001	1.17 (1.09–1.25)	<0.001
	≥5 d/wk	38 639	772	163 687	4.72	2.18 (2.03–2.35)	<0.001	1.18 (1.09–1.26)	<0.001
MetS-developed	0 d/wk	156 540	4347	634 581	6.85	3.17 (3.07–3.28)	<0.001	1.47 (1.43–1.53)	<0.001
	1–2 d/wk	101 511	1840	436 850	4.21	1.95 (1.86–2.05)	<0.001	1.41 (1.34–1.48)	<0.001
	3–4 d/wk	54 830	1084	231 489	4.68	2.17 (2.04–2.31)	<0.001	1.22 (1.14–1.3)	<0.001
	≥5 d/wk	35 282	922	143 535	6.42	2.97 (2.78–3.18)	<0.001	1.24 (1.16–1.33)	<0.001
MetS-chronic	0 d/wk	406 137	15 625	1 624 863	9.62	4.45 (4.36–4.55)	<0.001	1.60 (1.56–1.64)	<0.001
	1–2 d/wk	225 524	6096	965 660	6.31	2.92 (2.84–3.01)	<0.001	1.60 (1.55–1.65)	<0.001
	3–4 d/wk	136 733	3867	572 284	6.76	3.13 (3.02–3.24)	<0.001	1.37 (1.32–1.42)	<0.001
	≥5 d/wk	95 669	3219	384 603	8.37	3.88 (3.73–4.02)	<0.001	1.30 (1.25–1.35)	<0.001

Multivariable model was adjusted for baseline age, sex, estimated glomerular filtration rate (continuous, mL/min per 1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m2), Charlson Comorbidity Index score, and place of residence (urban or rural). IRR indicates incidence rate ratio; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; and MV-PA, moderate-to-vigorous physical activity.

Table 3. Risks of All-Cause Mortality According to the Frequency of Moderate-to-Vigorous Physical Activity and MetS Status

MetS status	Frequency of MV-PA	Number of People	Number of Death	Follow-Up (Person-Years)	Incidence Rate (/1000 Person-Years)	Unadjusted Model		Multivariable Model	
						IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
MetS-free	0 d/wk	1 840 026	15 621	8 012 877	1.95	Reference		Reference	
	1–2 d/wk	1 531 152	6733	6 896 304	0.98	0.50 (0.49–0.52)	<0.001	0.79 (0.77–0.82)	<0.001
	3–4 d/wk	756 270	4145	3 377 828	1.23	0.63 (0.61–0.65)	<0.001	0.77 (0.74–0.80)	<0.001
	≥5 d/wk	420 090	3559	1 832 813	1.94	1.00 (0.96–1.03)	0.832	0.82 (0.79–0.85)	<0.001
MetS-recovery	0 d/wk	145 047	2376	616 827	3.85	1.98 (1.89–2.06)	<0.001	1.24 (1.19–1.29)	<0.001
	1–2 d/wk	104 911	760	470 783	1.61	0.83 (0.77–0.89)	<0.001	0.89 (0.82–0.95)	0.001
	3–4 d/wk	59 716	526	264 399	1.99	1.02 (0.94–1.11)	0.647	0.88 (0.80–0.96)	0.003
	≥5 d/wk	38 639	489	165 185	2.96	1.52 (1.39–1.66)	<0.001	0.90 (0.82–0.99)	0.025
MetS-developed	0 d/wk	156 540	2467	642 750	3.84	1.97 (1.89–2.05)	<0.001	1.10 (1.06–1.15)	<0.001
	1–2 d/wk	101 511	933	440 524	2.12	1.09 (1.02–1.16)	0.014	1.03 (0.97–1.10)	0.342
	3–4 d/wk	54 830	550	233 594	2.35	1.21 (1.11–1.31)	<0.001	0.85 (0.78–0.92)	<0.001
	≥5 d/wk	35 282	472	145 281	3.25	1.67 (1.52–1.83)	<0.001	0.79 (0.72–0.87)	<0.001
MetS-chronic	0 d/wk	406 137	7601	1 654 198	4.59	2.36 (2.29–2.42)	<0.001	1.09 (1.06–1.13)	<0.001
	1–2 d/wk	225 524	2368	977 978	2.42	1.24 (1.19–1.30)	<0.001	0.92 (0.88–0.96)	<0.001
	3–4 d/wk	136 733	1663	579 996	2.87	1.470 (1.4–1.55)	<0.001	0.83 (0.79–0.87)	<0.001
	≥5 d/wk	95 669	1577	390 821	4.04	2.07 (1.97–2.18)	<0.001	0.84 (0.80–0.89)	<0.001

Multivariable model was adjusted for baseline age, sex, estimated glomerular filtration rate (continuous, mL/min per 1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m2), Charlson Comorbidity Index score, and place of residence (urban or rural). IRR indicates incidence rate ratio; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; and MV-PA, moderate-to-vigorous physical activity.

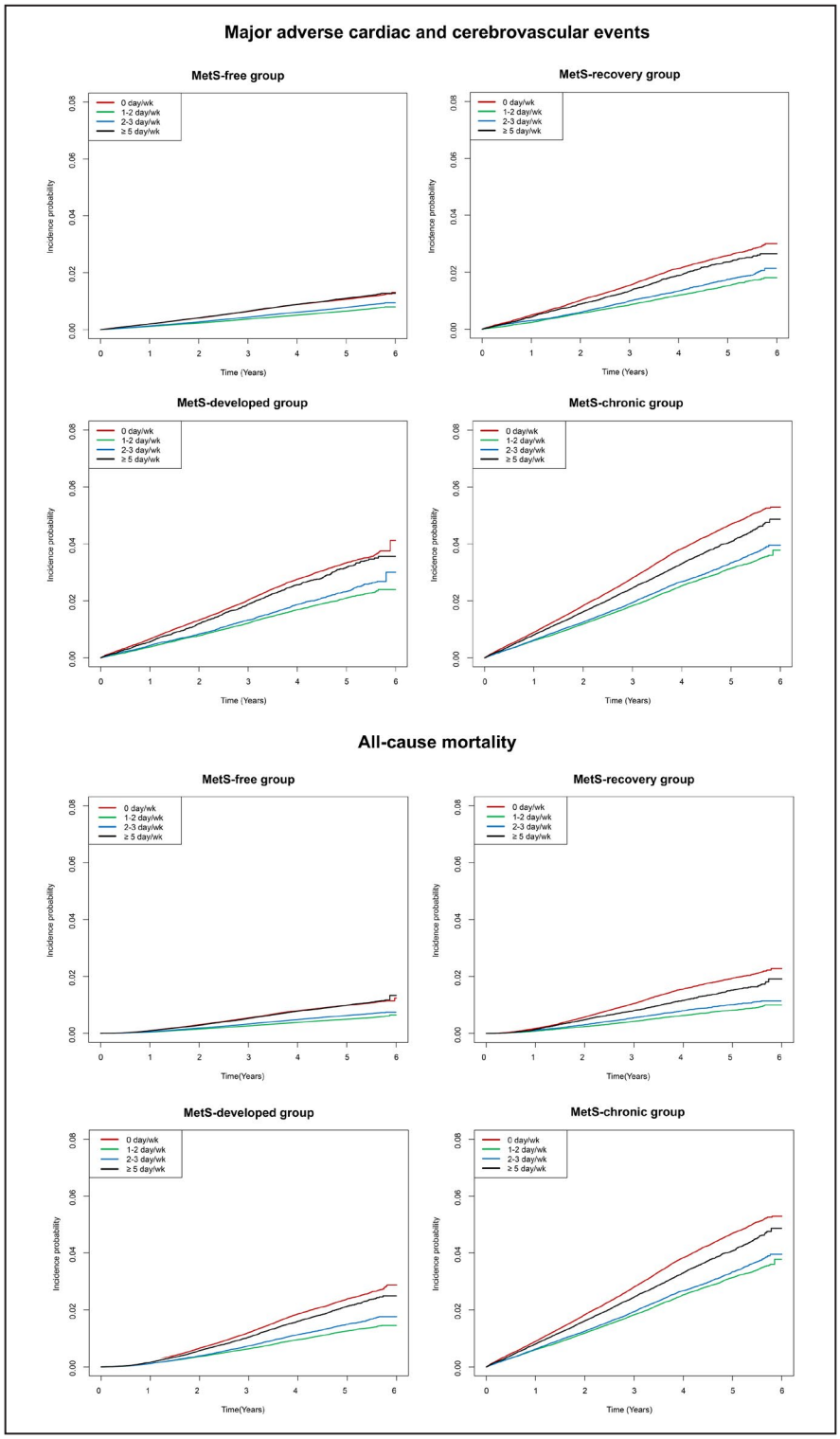

Figure 2. Kaplan–Meier survival curve plotting the incidence probability of major adverse cardiovascular events and all-cause mortality according to the frequency of self-reported moderate-to-vigorous physical activity.

The survival curves were plotted in each metabolic syndrome subgroup. The *y*-axes indicate the incidence probability of major adverse cardiovascular events and all-cause mortality. The *x*-axes indicate the time (years). The tables below the survival curves show the numbers of people at risk. MetS indicates metabolic syndrome; and MV-PA, moderate-to-vigorous physical activity.

Table 4. Risks of Major Adverse Cardiovascular Events According to the Frequency of Moderate-to-Vigorous Physical Activity in Each Study Group

Subgroups and Exposure	Model 1. Adjusted for the Baseline Severity of MetS (Number of MetS Components)*		Model 2. Adjusted for the Baseline Severity of MetS (Laboratory Parameters of MetS)†		Model 3. Adjusted for the Baseline Severity of MetS (Number of MetS Components) and Other Lifestyle Variables (Smoking, Alcohol)‡	
	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
MetS-free						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.92 (0.89–0.94)	<0.001	0.91 (0.89–0.94)	<0.001	0.94 (0.92–0.97)	<0.001
3–4 d/wk	0.83 (0.81–0.86)	<0.001	0.84 (0.81–0.87)	<0.001	0.87 (0.84–0.90)	<0.001
≥5 d/wk	0.82 (0.80–0.85)	<0.001	0.84 (0.81–0.87)	<0.001	0.86 (0.83–0.89)	<0.001
MetS-recovery						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.87 (0.81–0.93)	<0.001	0.87 (0.82–0.93)	<0.001	0.89 (0.84–0.95)	<0.001
3–4 d/wk	0.82 (0.77–0.89)	<0.001	0.83 (0.77–0.89)	<0.001	0.87 (0.80–0.93)	<0.001
≥5 d/wk	0.83 (0.77–0.91)	<0.001	0.84 (0.78–0.91)	<0.001	0.87 (0.81–0.94)	<0.001
MetS-developed						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.90 (0.85–0.95)	<0.001	0.91 (0.86–0.96)	<0.001	0.92 (0.87–0.98)	0.006
3–4 d/wk	0.81 (0.75–0.86)	<0.001	0.81 (0.76–0.86)	<0.001	0.84 (0.78–0.90)	<0.001
≥5 d/wk	0.85 (0.79–0.91)	<0.001	0.86 (0.80–0.92)	<0.001	0.88 (0.82–0.95)	<0.001
MetS-chronic						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.92 (0.89–0.95)	<0.001	0.93 (0.90–0.95)	<0.001	0.94 (0.91–0.97)	<0.001
3–4 d/wk	0.82 (0.79–0.85)	<0.001	0.83 (0.81–0.86)	<0.001	0.85 (0.82–0.88)	<0.001
≥5 d/wk	0.82 (0.79–0.85)	<0.001	0.84 (0.81–0.87)	<0.001	0.85 (0.82–0.89)	<0.001

IRR indicates incidence rate ratio; and MetS, metabolic syndrome.

*Model 1 was adjusted for age, sex, baseline estimated glomerular filtration rate (continuous, mL/min per 1.73 m^2), alanine aminotransferase (continuous, IU/mL aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

†Model 2 was adjusted for the same variables as Model 1, but the exact values of waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, and high-density lipoprotein cholesterol were included in the multivariable model instead of the number of MetS components.

‡Model 3 was adjusted for the same variables as Model 1, but other lifestyle variables (smoking: none, previous, and current; alcohol consumption: none, moderate, heavy) were additionally included.

week was associated with a 12% to 16% lower risk of MACEs 14% to 25% lower risk for all-cause mortality, respectively, when compared with those who did not engage in MV-PA.

Subgroup Analysis Results

When we stratified the subjects according to age being engaged on MV-PA was generally associated with lower risk of MACE (Tables S4 through S6) or all-cause mortality (Tables S7 through S9) in the middle (40–64 years old) and the old age (≥65 years old) subgroups but not in the young age (20–39 years old) subgroup. Regarding sex, although the overall incidence rate for MACE (Tables S10 and S11) or death rates (Tables S12 and S13) were lower in the females, MV-PA was associated significantly lower adverse outcome risks in both sexes except for few associations with marginal significance. When we tested the association between the frequency of MV-PA and MACE or all-cause mortality risks in 1 297 589 individuals with undetermined MetS status (Table S14), who were initially excluded in the main analysis, the results were similar (Table S15). When we assessed this association in each subgroup with a consistently absent or present state of each individual MetS component, a similar result was identified (Tables S16 and S17), and MV-PA was associated with lower MACE or all-cause mortality risks in all subgroups after clinicodemographic characteristics were adjusted.

DISCUSSION

In this nationwide study, we found that the beneficial association of MV-PA with the risk of MACE or all-cause mortality was present in individuals with various dynamic status of MetS regardless of MetS severity.

Table 5. Risks of All-Cause Mortality According to the Frequency of Moderate-to-Vigorous Physical Activity in Each Study Group

Subgroups and Exposure	Model 1. Adjusted for the Baseline Severity of MetS (Number of MetS Components)*		Model 2. Adjusted for the Baseline Severity of MetS (Laboratory Parameters of MetS)†		Model 3. Adjusted for the Baseline Severity of MetS (Number of MetS Components) and Other Lifestyle Variables (Smoking, Alcohol)‡	
	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
MetS-free						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.82 (0.8–0.85)	<0.001	0.82 (0.8–0.84)	<0.001	0.85 (0.82–0.87)	<0.001
3–4 d/wk	0.79 (0.76–0.82)	<0.001	0.8 (0.77–0.82)	<0.001	0.83 (0.8–0.86)	<0.001
≥5 d/wk	0.82 (0.79–0.86)	<0.001	0.83 (0.8–0.87)	<0.001	0.86 (0.83–0.89)	<0.001
MetS-recovery						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.72 (0.66–0.79)	<0.001	0.72 (0.66–0.78)	<0.001	0.74 (0.68–0.81)	<0.001
3–4 d/wk	0.72 (0.65–0.79)	<0.001	0.71 (0.65–0.79)	<0.001	0.75 (0.68–0.83)	<0.001
≥5 d/wk	0.74 (0.67–0.81)	<0.001	0.73 (0.66–0.81)	<0.001	0.77 (0.7–0.85)	<0.001
MetS-developed						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.89 (0.82–0.96)	0.002	0.88 (0.81–0.95)	0.001	0.91 (0.84–0.99)	0.024
3–4 d/wk	0.73 (0.66–0.8)	<0.001	0.76 (0.69–0.83)	<0.001	0.77 (0.7–0.84)	<0.001
≥5 d/wk	0.71 (0.64–0.79)	<0.001	0.75 (0.68–0.83)	<0.001	0.75 (0.68–0.83)	<0.001
MetS-chronic						
0 d/wk	Reference		Reference		Reference	
1–2 d/wk	0.81 (0.77–0.85)	<0.001	0.82 (0.78–0.86)	<0.001	0.83 (0.79–0.87)	<0.001
3–4 d/wk	0.73 (0.69–0.77)	<0.001	0.77 (0.72–0.81)	<0.001	0.76 (0.72–0.81)	<0.001
≥5 d/wk	0.77 (0.73–0.82)	<0.001	0.81 (0.76–0.85)	<0.001	0.81 (0.77–0.85)	<0.001

IRR indicates incidence rate ratio; and MetS, metabolic syndrome.

*Model 1 was adjusted for age, sex, baseline estimated glomerular filtration rate (continuous, mL/min per 1.73 m^2), alanine aminotransferase (continuous, IU/mL aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

†Model 2 was adjusted for the same variables as Model 1, but the exact values of waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, and high-density lipoprotein cholesterol were included in the multivariable model instead of the number of MetS components.

‡Model 3 was adjusted for the same variables as Model 1, but other lifestyle variables (smoking: none, previous, current; and alcohol consumption: none, moderate, heavy) were additionally included.

Those who engaged in MV-PA had a better cardiovascular outcome and survival than those who did not MV-PA among those who remained free from MetS or had already recovered from MetS. Also, in the population who had or developed MetS, a lower risk of MACE or all-cause mortality was identified in those who MV-PA, even after controlling for the baseline severity of MetS. Our study provides population-scale evidence that supports encouraging MV-PA in all people regardless of their metabolic risk profiles.

Managing metabolic risk factors is the mainstay of the current method of reducing the risk of MACEs or mortality.[9,20,21] We also reported a population-scale study that showed that recovery from or the development of MetS is associated with altered risks of MACE, further highlighting the importance of the controlling or prevention of MetS.[11] MV-PA has been acknowledged as one of the main lifestyle improvements to ameliorate MetS and further reduce the risk of MACEs or deaths.[9] However, there have been remaining questions regarding whether targeting metabolic risk profiles is the sole beneficial effect of MV-PA on the cardiovascular system, as certain aspects of adverse outcome risks are not explained by the metabolic profiles.[13,14] To determine whether MV-PA has benefits in the general population with various MetS status, we performed this study, and the results suggest that there may be certain benefits of MV-PA independent of MetS status or severity. Our study has strengths in that (1) we successfully stratified the dynamic MetS status of ≈6 million people by analyzing a unique nationwide cohort who underwent successive health screenings, (2) a self-reported questionnaire was administered to a large number of people, and (3) we showed that MV-PA was associated with lower actual MACE or all-cause mortality risks, not just reduced individual MetS

parameters, in the general population. Therefore, according to our study results, healthcare providers may encourage MV-PA to reduce the risk of MACEs or all-cause mortality in people regardless of their current or recent metabolic risk status.

Based on our results, MV-PA may be recommended even for those who are free from or already recovered from MetS, and the MetS-free population who engages in MV-PA may have an even lower risk of MACE or deaths than people who are free from MetS but do not participate in MV-PA. Namely, the absence of metabolic risk factors may not indicate that there is a limited advantage of MV-PA with regard to cardiovascular health for such people who are MetS free. In our previous report,[11] MetS recovery was associated with an ≈20% lower adjusted risk of MACE or all-cause mortality when compared with those who remained in the chronic MetS state. The current study suggests that those who engage in MV-PA may have even lower adverse outcome risks after their recovery than those who do not. The overall MACE or all-cause mortality risks were higher in those with MetS than in those without MetS; however, MV-PA was still related to lower MACE or death risks in those with MetS. It is common for people to still have MetS even though they engage in MV-PA, and prominent improvements in measurable MetS parameters are not easily achieved through lifestyle modifications in the real world. Our study shows that even in people with chronic MetS, MV-PA should be consistently recommended to at least partially reduce their high risk of MACEs and all-cause mortality.

Although controlling metabolic risk factors has been considered the main mechanism underlying the benefits of MV-PA, there are other effects of MV-PA on the cardiovascular system (eg, improvement in vascular remodeling,[22,23] cardiac adaptation,[24] and MV-PA-induced adaptations[25]). As such beneficial effects may not be directly reflected in measurable laboratory parameters, our study results can serve as large-scale clinical evidence that those nontraditional mechanisms may actually lead to a better cardiovascular prognosis. In addition, a future study investigating the benefits of MV-PA on cardiovascular disease may further elucidate the various mechanisms through which the benefits of MV-PA occur.[13,14] Particularly, as in our study results, those with middle or old age, rather than those with young age, would be the primary target group of interest for a such trial.

Our study has several limitations. First, a retrospective study based on a claims database innately has limited sensitivity, so missed events or confounders may be present. Second, although the questionnaire was relatively simple, the accuracy of the questionnaire has not been validated, and we were able to study only "self-reported" frequencies of MV-PA. Additional studies regarding the types or intensities of MV-PA in detail may provide specific recommendations for how the risk of MACE is effectively reduced by MV-PA. Third, although the study included one of the largest nationwide cohorts with reported frequencies of MV-PA, the follow-up duration was relatively short. Last, the study examined a population in a single nation with limited ethnic diversity, so whether the results can be generalized to other countries is unknown.

In conclusion, MV-PA is associated with a lower MACE and all-cause mortality risk in general people regardless of their previous or current MetS status. Healthcare providers should emphasize the importance of MV-PA for people even if they are free from MetS or have already recovered from MetS. In those with worsening metabolic health or no obvious improvements in metabolic health, MV-PA may still be recommended, as certain benefits of MV-PA may be independent of the status of measurable MetS parameters.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1–S2
Tables S1–S17
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Details regarding data collection.

Collected clinicodemographic variables

The following information was collected at the third health screening (S3) as baseline characteristics: age, sex, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, serum creatinine, estimated glomerular filtration rate, alanine transaminase, aspartate transaminase, and hemoglobin. Those who were included in the lowest quartile of the nation's income were defined as the low-income group. The Charlson Comorbidity Index was used to represent the burden of underlying comorbidities in the included people. A diagnostic code category identified multiple times within a year before the baseline health screening (S3) was considered to indicate a comorbidity, and the definition for the diagnostic codes followed a reference.[26] The number of present MetS components was collected, both at baseline (S3) and at a prior health screening (S1), to describe the metabolic burden in each study subgroup. We also collected other lifestyle variables from the questionnaire results: smoking (non-smoker, ex-smoker, and current smoker) and alcohol consumption [none, moderate consumption ($\leq$ 2 standard drinks for men and $\leq$ 1 standard drink for women per single session), and heavy consumption (more than moderate)]. Places of residence (rural or urban), and the urban region was the capital region and 7 metropolitan cities, and the other regions were categorized as rural area.

Variables representing the severity of MetS

The severity of MetS as a covariate was defined, as the metabolic burden can be diverse even within a study subgroup, according to the following two aspects: the number of MetS components present and the actual measured values of the components included in the MetS criteria. The two aspects were complementary because the number of preexisting MetS components could not reflect the continuous information (e.g., high glucose values) pertaining to each MetS parameter, and the actual values of the MetS parameters could be affected by medications.

Data S2.

Details regarding the adjustment variables for multivariable analyses.

Continuous variables are presented as the mean values (standard deviations), and categorical variables are presented as numbers (percentages).

In the first analysis, comparing the risk of MACEs or all-cause mortality in each study subgroup divided according to the dynamic MetS status and frequency of MV-PA, the MetS-free group with 0 days/week of self-reported MV-PA was the reference group. As the other clinical characteristics would be distinct in each subgroup (e.g., a higher body mass index in the MetS-chronic group or a lower comorbidity burden in the MetS-free group), the multivariable model in the first analysis was adjusted for baseline age, sex, eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, and place of residence (urban or rural). The results comparing the MetS subgroups in detail have been reported in our previous study,[1] with further consideration of other important potential confounders.

In the second analysis, the association between the frequency of MV-PA and the risk of MACE or all-cause mortality in each MetS subgroup was assessed, with those who did not engage in MV-PA in each subgroup serving as the reference group. The main purpose of this analysis was to assess whether MV-PA was related to a lower MACE or all-cause mortality risk in those with similar clinical and metabolic status. Therefore, additional clinical variables were used to adjust the models, including the MetS severity. The model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index, Charlson Comorbidity Index score, place of residence, and MetS severity. The MetS severity was determined as the number of MetS components or the actual values of the MetS components. In addition, as smoking or alcohol consumption behaviors might also confound the association, the lifestyle variables were additionally adjusted in a model. Further subgroup analyses were performed, and the

subgroups were divided according to age (20-39, 40-64, ≥ 65 years old) or sex (male or female). Additional subgroup analysis was performed for the initially excluded subjects due to their fluctuating/transient MetS status (N = 1,544,500). Those who had impaired kidney function or previous MACE history were again not considered in the subgroup analysis, yielding 1,297,589 subjects with transient/fluctuating MetS status in the analysis. The multivariable results for the subgroup analyses were adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

In the third analysis, we divided the study population according to whether they had a consistently absent (absence in S1, S2, and S3) or present (presence in S1, S2, and S3) states of individual MetS components (central obesity, high blood pressure, impaired glucose tolerance, high triglyceride, low high-density lipoprotein cholesterol). The purpose of this analysis was to additionally test the significance of MV-PA for each MetS component, as MetS is a cluster of 5 risk components and the significance of MV-PA may vary according to the components. In the analysis, those who were initially excluded due to their fluctuating/transient status of MetS were included, and the dynamic status of each MetS component was re-assessed. The unadjusted and age-/sex-adjusted models were first constructed. In addition, a multivariable model adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index, Charlson Comorbidity Index score, place of residences (urban or rural), MetS severity represented by the number of MetS components, and other lifestyle variables (smoking status and alcohol consumption behavior) was presented. Those who developed a component or recovered from a previous presence of a MetS component were not separately analyzed, as the total number of persons and outcomes in each subgroup was small when we divided subgroups in this manner.

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Table S1. Risks of acute myocardial infarction according to frequency of moderate-to-vigorous physical activity and dynamic metabolic syndrome status.

MetS status	Frequency of MV-PA	Number of persons	Number of acute MI	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	1,840,026	5,521	7,981,116	0.69	Reference		Reference	
	1-2 days/week	1,531,152	3,086	6,878,663	0.45	0.65 (0.62-0.68)	< 0.001	0.81 (0.78-0.85)	< 0.001
	3-4 days/week	756,270	1,700	3,367,586	0.50	0.73 (0.69-0.77)	< 0.001	0.77 (0.72-0.81)	< 0.001
	≥5 days/week	420,090	1,234	1,825,140	0.68	0.98 (0.92-1.04)	0.468	0.81 (0.76-0.87)	< 0.001
MetS-recovery	0 days/week	145,047	969	610,910	1.59	2.29 (2.14-2.45)	< 0.001	1.43 (1.34-1.53)	< 0.001
	1-2 days/week	104,911	474	468,051	1.01	1.46 (1.33-1.61)	< 0.001	1.24 (1.13-1.36)	< 0.001
	3-4 days/week	59,716	278	262,637	1.06	1.53 (1.36-1.73)	< 0.001	1.12 (0.99-1.26)	0.067
	≥5 days/week	38,639	217	163,687	1.33	1.92 (1.67-2.19)	< 0.001	1.11 (0.97-1.28)	0.123
MetS-developed	0 days/week	156,540	1,264	634,582	1.99	2.88 (2.71-3.06)	< 0.001	1.50 (1.41-1.60)	< 0.001
	1-2 days/week	101,511	566	436,851	1.30	1.87 (1.72-2.04)	< 0.001	1.35 (1.24-1.47)	< 0.001
	3-4 days/week	54,830	338	231,489	1.46	2.11 (1.89-2.36)	< 0.001	1.24 (1.11-1.39)	< 0.001
	≥5 days/week	35,282	248	143,535	1.73	2.5 (2.20-2.84)	< 0.001	1.17 (1.03-1.32)	0.019
MetS-chronic	0 days/week	406,137	4,088	1,624,864	2.52	3.64 (3.49-3.79)	< 0.001	1.51 (1.44-1.58)	< 0.001
	1-2 days/week	225,524	1,871	965,660	1.94	2.80 (2.66-2.95)	< 0.001	1.59 (1.51-1.68)	< 0.001
	3-4 days/week	136,733	1,051	572,285	1.84	2.65 (2.49-2.84)	< 0.001	1.26 (1.18-1.35)	< 0.001
	≥5 days/week	95,669	811	384,604	2.11	3.05 (2.83-3.28)	< 0.001	1.18 (1.09-1.27)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, MI = myocardial infarction, IRR = incidence rate ratio, CI = confidence interval
The multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, and place of residence (urban or rural).

Table S2. Risks of revascularization according to frequency of moderate-to-vigorous physical activity and dynamic metabolic syndrome status.

MetS status	Frequency of MV-PA	Number of persons	Number of revascularization	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	1,840,026	4,257	7,981,116	0.53	Reference		Reference	
	1-2 days/week	1,531,152	2,702	6,878,663	0.39	0.74 (0.70-0.77)	< 0.001	0.91 (0.87-0.96)	< 0.001
	3-4 days/week	756,270	1,618	3,367,586	0.48	0.90 (0.85-0.95)	< 0.001	0.92 (0.86-0.97)	0.003
	≥5 days/week	420,090	1,198	1,825,140	0.66	1.23 (1.15-1.31)	< 0.001	0.95 (0.89-1.02)	0.137
MetS-recovery	0 days/week	145,047	936	610,910	1.53	2.87 (2.68-3.08)	< 0.001	1.71 (1.59-1.83)	< 0.001
	1-2 days/week	104,911	525	468,051	1.12	2.10 (1.92-2.30)	< 0.001	1.62 (1.48-1.78)	< 0.001
	3-4 days/week	59,716	320	262,637	1.22	2.28 (2.04-2.56)	< 0.001	1.51 (1.35-1.69)	< 0.001
	≥5 days/week	38,639	266	163,687	1.63	3.05 (2.69-3.45)	< 0.001	1.56 (1.38-1.76)	< 0.001
MetS-developed	0 days/week	156,540	1,303	634,582	2.05	3.85 (3.62-4.10)	< 0.001	1.97 (1.85-2.10)	< 0.001
	1-2 days/week	101,511	756	436,851	1.73	3.24 (3.00-3.51)	< 0.001	2.16 (1.99-2.33)	< 0.001
	3-4 days/week	54,830	440	231,489	1.90	3.56 (3.23-3.93)	< 0.001	1.93 (1.75-2.13)	< 0.001
	≥5 days/week	35,282	338	143,535	2.35	4.41 (3.95-4.93)	< 0.001	1.86 (1.67-2.08)	< 0.001
MetS-chronic	0 days/week	406,137	5,127	1,624,864	3.16	5.92 (5.68-6.16)	< 0.001	2.50 (2.39-2.61)	< 0.001
	1-2 days/week	225,524	2,613	965,660	2.71	5.07 (4.83-5.33)	< 0.001	2.67 (2.53-2.81)	< 0.001
	3-4 days/week	136,733	1,626	572,285	2.84	5.33 (5.03-5.64)	< 0.001	2.35 (2.22-2.50)	< 0.001
	≥5 days/week	95,669	1,281	384,604	3.33	6.24 (5.87-6.65)	< 0.001	2.21 (2.07-2.36)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

The multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, and place of residence (urban or rural).

Table S3. Risks of acute ischemic stroke according to frequency of moderate-to-vigorous physical activity and dynamic metabolic syndrome status.

MetS status	Frequency of MV-PA	Number of persons	Number of acute ischemic stroke	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	1,840,026	9,414	7,981,116	1.18	Reference		Reference	
	1-2 days/week	1,531,152	4,353	6,878,663	0.63	0.54 (0.52-0.56)	< 0.001	0.83 (0.80-0.87)	< 0.001
	3-4 days/week	756,270	2,605	3,367,586	0.77	0.66 (0.63-0.68)	< 0.001	0.78 (0.75-0.81)	< 0.001
	≥5 days/week	420,090	2,093	1,825,140	1.15	0.97 (0.93-1.02)	0.244	0.81 (0.77-0.85)	< 0.001
MetS-recovery	0 days/week	145,047	1,748	610,910	2.86	2.43 (2.31-2.55)	< 0.001	1.32 (1.26-1.39)	< 0.001
	1-2 days/week	104,911	678	468,051	1.45	1.23 (1.14-1.33)	< 0.001	1.15 (1.06-1.24)	< 0.001
	3-4 days/week	59,716	438	262,637	1.67	1.41 (1.28-1.56)	< 0.001	1.06 (0.97-1.17)	0.199
	≥5 days/week	38,639	397	163,687	2.43	2.06 (1.86-2.27)	< 0.001	1.09 (0.99-1.21)	0.082
MetS-developed	0 days/week	156,540	2,339	634,582	3.69	3.12 (2.99-3.27)	< 0.001	1.34 (1.28-1.41)	< 0.001
	1-2 days/week	101,511	837	436,851	1.92	1.62 (1.51-1.74)	< 0.001	1.22 (1.14-1.31)	< 0.001
	3-4 days/week	54,830	489	231,489	2.11	1.79 (1.64-1.96)	< 0.001	1.00 (0.92-1.10)	0.933
	≥5 days/week	35,282	454	143,535	3.16	2.68 (2.44-2.95)	< 0.001	1.07 (0.97-1.17)	0.176
MetS-chronic	0 days/week	406,137	8,274	1,624,864	5.09	4.32 (4.19-4.45)	< 0.001	1.39 (1.34-1.44)	< 0.001
	1-2 days/week	225,524	2,688	965,660	2.78	2.36 (2.26-2.46)	< 0.001	1.29 (1.24-1.35)	< 0.001
	3-4 days/week	136,733	1,791	572,285	3.13	2.65 (2.52-2.79)	< 0.001	1.12 (1.07-1.18)	< 0.001
	≥5 days/week	95,669	1,528	384,604	3.97	3.37 (3.19-3.56)	< 0.001	1.06 (1.00-1.12)	0.054

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

The multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, and place of residence (urban or rural).

Table S4. Risks of major adverse cardiovascular events according to the frequency of moderate-to-vigorous physical activity in each study group within subjects with age 20-39 years old.

MetS status	Frequency of MV-PA	Number of persons	Number of MACE	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	703,712	1,012	3,216,593	0.31	Reference		Reference	
	1-2 days/week	714,886	1,101	3,306,908	0.33	1.06 (0.97-1.15)	0.19	1.01 (0.93-1.1)	0.82
	3-4 days/week	275,702	428	1,284,732	0.33	1.06 (0.95-1.19)	0.32	1.02 (0.91-1.14)	0.78
	≥5 days/week	121,386	176	565,971	0.31	0.99 (0.84-1.16)	0.89	0.96 (0.82-1.13)	0.63
MetS-recovery	0 days/week	25,987	82	120,679	0.68	Reference		Reference	
	1-2 days/week	30,272	97	142,395	0.68	1 (0.75-1.35)	0.99	0.96 (0.72-1.3)	0.81
	3-4 days/week	12,780	54	60,557	0.89	1.31 (0.93-1.85)	0.12	1.33 (0.94-1.89)	0.10
	≥5 days/week	5,936	21	27,984	0.75	1.1 (0.68-1.78)	0.69	1.18 (0.73-1.91)	0.51
MetS-developed	0 days/week	20,426	98	92,136	1.06	Reference		Reference	
	1-2 days/week	24,477	119	111,780	1.06	1 (0.77-1.31)	0.99	0.99 (0.76-1.3)	0.96
	3-4 days/week	8,175	41	37,771	1.09	1.02 (0.71-1.47)	0.91	1.04 (0.72-1.51)	0.82
	≥5 days/week	3,102	18	14,372	1.25	1.18 (0.71-1.95)	0.52	1.24 (0.75-2.06)	0.40
MetS-chronic	0 days/week	28,739	206	131,534	1.57	Reference		Reference	
	1-2 days/week	36,795	274	170,383	1.61	1.03 (0.86-1.23)	0.77	1.02 (0.85-1.22)	0.87
	3-4 days/week	13,024	102	61,088	1.67	1.07 (0.84-1.35)	0.60	1.03 (0.81-1.32)	0.78
	≥5 days/week	4,989	40	23,282	1.72	1.1 (0.78-1.54)	0.59	1.09 (0.78-1.54)	0.61

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S5. Risks of major adverse cardiovascular events according to the frequency of moderate-to-vigorous physical activity in each study group within subjects with age 40-64 years old.

MetS status	Frequency of MV-PA	Number of persons	Number of MACE	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	976,905	8,871	4,163,437	2.13	Reference		Reference	
	1-2 days/week	770,823	6,169	3,396,451	1.82	0.85 (0.83-0.88)	< 0.001	0.92 (0.89-0.95)	< 0.001
	3-4 days/week	439,019	3,468	1,922,719	1.80	0.85 (0.81-0.88)	< 0.001	0.84 (0.8-0.87)	< 0.001
	≥5 days/week	252,297	2,232	1,083,420	2.06	0.97 (0.92-1.01)	0.16	0.86 (0.82-0.9)	< 0.001
MetS-recovery	0 days/week	90,232	1,594	382,771	4.16	Reference		Reference	
	1-2 days/week	67,267	955	297,656	3.21	0.77 (0.71-0.83)	< 0.001	0.83 (0.76-0.9)	< 0.001
	3-4 days/week	40,246	587	176,549	3.32	0.8 (0.73-0.88)	< 0.001	0.8 (0.73-0.88)	< 0.001
	≥5 days/week	25,033	406	106,888	3.80	0.91 (0.82-1.02)	0.10	0.83 (0.74-0.93)	< 0.001
MetS-developed	0 days/week	96,352	1,988	395,779	5.02	Reference		Reference	
	1-2 days/week	67,144	1,211	288,122	4.20	0.84 (0.78-0.9)	< 0.001	0.87 (0.81-0.94)	< 0.001
	3-4 days/week	37,707	680	160,224	4.24	0.84 (0.77-0.92)	< 0.001	0.83 (0.76-0.9)	< 0.001
	≥5 days/week	22,755	466	94,298	4.94	0.98 (0.89-1.09)	0.75	0.89 (0.8-0.98)	0.02
MetS-chronic	0 days/week	236,590	6,630	975,632	6.80	Reference		Reference	
	1-2 days/week	155,107	3,921	670,350	5.85	0.86 (0.83-0.9)	< 0.001	0.9 (0.87-0.94)	< 0.001
	3-4 days/week	92,355	2,283	394,689	5.78	0.85 (0.81-0.89)	< 0.001	0.83 (0.79-0.87)	< 0.001
	≥5 days/week	57,905	1,459	240,775	6.06	0.89 (0.84-0.94)	< 0.001	0.82 (0.78-0.87)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S6. Risks of major adverse cardiovascular events according to the frequency of moderate-to-vigorous physical activity in each study group within subjects with age ≥ 65 years old.

MetS status	Frequency of MV-PA	Number of persons	Number of MACE	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	159,409	7,354	601,086	12.23	Reference		Reference	
	1-2 days/week	45,443	1,683	175,303	9.60	0.78 (0.74-0.83)	< 0.001	0.86 (0.82-0.91)	< 0.001
	3-4 days/week	41,549	1,330	160,135	8.31	0.68 (0.64-0.72)	< 0.001	0.76 (0.71-0.8)	< 0.001
	≥5 days/week	46,407	1,619	175,750	9.21	0.75 (0.71-0.79)	< 0.001	0.77 (0.73-0.81)	< 0.001
MetS-recovery	0 days/week	28,828	1,546	107,460	14.39	Reference		Reference	
	1-2 days/week	7,372	371	28,000	13.25	0.92 (0.82-1.03)	0.15	0.95 (0.84-1.06)	0.34
	3-4 days/week	6,690	269	25,531	10.54	0.73 (0.64-0.83)	< 0.001	0.78 (0.69-0.89)	< 0.001
	≥5 days/week	7,670	345	28,816	11.97	0.83 (0.74-0.94)	0.002	0.83 (0.73-0.93)	0.002
MetS-developed	0 days/week	39,762	2,261	146,666	15.42	Reference		Reference	
	1-2 days/week	9,890	510	36,948	13.80	0.9 (0.81-0.99)	0.02	0.94 (0.85-1.04)	0.21
	3-4 days/week	8,948	363	33,494	10.84	0.7 (0.63-0.79)	< 0.001	0.75 (0.67-0.83)	< 0.001
	≥5 days/week	9,425	438	34,865	12.56	0.81 (0.74-0.9)	< 0.001	0.81 (0.73-0.9)	< 0.001
MetS-chronic	0 days/week	140,808	8,789	517,698	16.98	Reference		Reference	
	1-2 days/week	33,622	1,901	124,928	15.22	0.9 (0.85-0.94)	< 0.001	0.93 (0.89-0.98)	0.006
	3-4 days/week	31,354	1,482	116,507	12.72	0.75 (0.71-0.79)	< 0.001	0.79 (0.75-0.84)	< 0.001
	≥5 days/week	32,775	1,720	120,548	14.27	0.84 (0.8-0.89)	< 0.001	0.84 (0.79-0.88)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S7. Risks of all-cause mortality according to the frequency of moderate-to-vigorous physical activity in each study group within subjects with age 20-39 years old.

MetS status	Frequency of MV-PA	Number of persons	Number of deaths	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	703,712	1,236	3,218,583	0.38	Reference		Reference	
	1-2 days/week	714,886	1,154	3,309,093	0.35	0.91 (0.84-0.98)	0.02	0.88 (0.81-0.95)	0.001
	3-4 days/week	275,702	494	1,285,576	0.38	1.00 (0.90-1.11)	0.98	0.94 (0.85-1.05)	0.28
	≥5 days/week	121,386	240	566,333	0.42	1.10 (0.96-1.27)	0.16	1.01 (0.88-1.17)	0.84
MetS-recovery	0 days/week	25,987	51	120,847	0.42	Reference		Reference	
	1-2 days/week	30,272	57	142,574	0.40	0.95 (0.65-1.38)	0.78	0.92 (0.63-1.35)	0.68
	3-4 days/week	12,780	25	60,635	0.41	0.98 (0.61-1.58)	0.92	0.98 (0.61-1.59)	0.94
	≥5 days/week	5,936	17	28,025	0.61	1.44 (0.83-2.49)	0.20	1.45 (0.83-2.52)	0.19
MetS-developed	0 days/week	20,426	70	92,333	0.76	Reference		Reference	
	1-2 days/week	24,477	72	112,013	0.64	0.85 (0.61-1.18)	0.33	0.83 (0.6-1.15)	0.27
	3-4 days/week	8,175	27	37,838	0.71	0.94 (0.60-1.47)	0.790	0.85 (0.54-1.33)	0.48
	≥5 days/week	3,102	11	14,411	0.76	1.01 (0.53-1.90)	0.98	0.85 (0.44-1.66)	0.64
MetS-chronic	0 days/week	28,739	89	131,946	0.67	Reference		Reference	
	1-2 days/week	36,795	129	170,899	0.75	1.12 (0.85-1.47)	0.41	1.10 (0.84-1.45)	0.48
	3-4 days/week	13,024	42	61,291	0.69	1.02 (0.70-1.47)	0.93	0.92 (0.63-1.34)	0.68
	≥5 days/week	4,989	16	23,357	0.69	1.02 (0.60-1.73)	0.96	0.93 (0.55-1.6)	0.80

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S8. Risks of all-cause mortality according to the frequency of moderate-to-vigorous physical activity in each study group within subjects with age 40-64 years old.

MetS status	Frequency of MV-PA	Number of persons	Number of deaths	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	976,905	6,221	4,180,767	1.49	Reference		Reference	
	1-2 days/week	770,823	3,934	3,408,883	1.15	0.78 (0.75-0.81)	< 0.001	0.84 (0.80-0.87)	< 0.001
	3-4 days/week	439,019	2,293	1,929,731	1.19	0.80 (0.76-0.84)	< 0.001	0.80 (0.76-0.84)	< 0.001
	≥5 days/week	252,297	1,716	1,087,843	1.58	1.06 (1.00-1.12)	0.03	0.92 (0.88-0.97)	0.004
MetS-recovery	0 days/week	90,232	925	385,822	2.40	Reference		Reference	
	1-2 days/week	67,267	480	299,547	1.60	0.67 (0.60-0.75)	< 0.001	0.73 (0.65-0.82)	< 0.001
	3-4 days/week	40,246	279	177,731	1.57	0.65 (0.57-0.75)	< 0.001	0.68 (0.59-0.77)	< 0.001
	≥5 days/week	25,033	223	107,725	2.07	0.86 (0.75-1.00)	0.049	0.77 (0.67-0.90)	< 0.001
MetS-developed	0 days/week	96,352	899	399,819	2.25	Reference		Reference	
	1-2 days/week	67,144	549	290,656	1.89	0.84 (0.76-0.93)	0.001	0.89 (0.80-0.99)	0.03
	3-4 days/week	37,707	299	161,619	1.85	0.82 (0.72-0.94)	0.003	0.77 (0.67-0.87)	< 0.001
	≥5 days/week	22,755	219	95,233	2.30	1.02 (0.88-1.19)	0.77	0.84 (0.72-0.98)	0.023
MetS-chronic	0 days/week	236,590	2,496	989,194	2.52	Reference		Reference	
	1-2 days/week	155,107	1,289	678,683	1.90	0.75 (0.70-0.81)	< 0.001	0.78 (0.73-0.84)	< 0.001
	3-4 days/week	92,355	867	399,493	2.17	0.86 (0.80-0.93)	< 0.001	0.80 (0.74-0.86)	< 0.001
	≥5 days/week	57,905	624	243,869	2.56	1.01 (0.93-1.11)	0.76	0.87 (0.80-0.95)	0.002

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S9. Risks of all-cause mortality according to the frequency of moderate-to-vigorous physical activity in each study group within subjects with age ≥ 65 years old.

MetS status	Frequency of MV-PA	Number of persons	Number of deaths	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	159,409	8,164	613,527	13.31	Reference		Reference	
	1-2 days/week	45,443	1,645	178,328	9.22	0.69 (0.66-0.73)	< 0.001	0.81 (0.77-0.86)	< 0.001
	3-4 days/week	41,549	1,358	162,522	8.36	0.63 (0.59-0.67)	< 0.001	0.78 (0.74-0.83)	< 0.001
	≥5 days/week	46,407	1,603	178,636	8.97	0.67 (0.64-0.71)	< 0.001	0.75 (0.71-0.79)	< 0.001
MetS-recovery	0 days/week	28,828	1,400	110,159	12.71	Reference		Reference	
	1-2 days/week	7,372	223	28,662	7.78	0.61 (0.53-0.71)	< 0.001	0.67 (0.59-0.78)	< 0.001
	3-4 days/week	6,690	222	26,033	8.53	0.67 (0.58-0.77)	< 0.001	0.79 (0.68-0.91)	0.001
	≥5 days/week	7,670	249	29,435	8.46	0.67 (0.58-0.76)	< 0.001	0.71 (0.62-0.81)	< 0.001
MetS-developed	0 days/week	39,762	1,498	150,598	9.95	Reference		Reference	
	1-2 days/week	9,890	312	37,855	8.24	0.83 (0.73-0.94)	0.003	0.9 (0.80-1.02)	0.09
	3-4 days/week	8,948	224	34,137	6.56	0.66 (0.57-0.76)	< 0.001	0.72 (0.62-0.83)	< 0.001
	≥5 days/week	9,425	242	35,638	6.79	0.68 (0.60-0.78)	< 0.001	0.66 (0.58-0.76)	< 0.001
MetS-chronic	0 days/week	140,808	5,016	533,058	9.41	Reference		Reference	
	1-2 days/week	33,622	950	128,396	7.40	0.79 (0.73-0.84)	< 0.001	0.82 (0.76-0.88)	< 0.001
	3-4 days/week	31,354	754	119,212	6.32	0.67 (0.62-0.73)	< 0.001	0.70 (0.65-0.76)	< 0.001
	≥5 days/week	32,775	937	123,595	7.58	0.81 (0.75-0.86)	< 0.001	0.76 (0.71-0.82)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S10. Risks of major adverse cardiovascular events according to the frequency of moderate-to-vigorous physical activity in each study group within subjects within male subjects.

MetS status	Frequency of MV-PA	Number of persons	Number of MACE	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	930,237	11,817	4,132,793	2.86	Reference		Reference	
	1-2 days/week	968,312	6,996	4,456,336	1.57	0.55 (0.53-0.57)	< 0.001	0.92 (0.89-0.95)	< 0.001
	3-4 days/week	457,437	3,993	2,114,502	1.89	0.66 (0.64-0.68)	< 0.001	0.83 (0.80-0.86)	< 0.001
	≥5 days/week	252,775	3,118	1,135,773	2.75	0.96 (0.92-1.00)	0.04	0.82 (0.79-0.85)	< 0.001
MetS-recovery	0 days/week	82,818	2,093	359,770	5.82	Reference		Reference	
	1-2 days/week	79,227	1,126	361,219	3.12	0.54 (0.50-0.58)	< 0.001	0.84 (0.78-0.91)	< 0.001
	3-4 days/week	42,056	715	191,365	3.74	0.64 (0.59-0.70)	< 0.001	0.81 (0.75-0.89)	< 0.001
	≥5 days/week	25,752	599	112,314	5.33	0.92 (0.84-1.00)	0.06	0.83 (0.76-0.91)	< 0.001
MetS-developed	0 days/week	80,162	2,521	337,783	7.46	Reference		Reference	
	1-2 days/week	73,896	1,414	327,046	4.32	0.58 (0.54-0.62)	< 0.001	0.90 (0.84-0.96)	0.001
	3-4 days/week	35,099	785	155,125	5.06	0.68 (0.63-0.73)	< 0.001	0.80 (0.74-0.87)	< 0.001
	≥5 days/week	20,448	657	86,568	7.59	1.02 (0.93-1.11)	0.70	0.86 (0.78-0.93)	< 0.001
MetS-chronic	0 days/week	182,679	7,615	766,556	9.93	Reference		Reference	
	1-2 days/week	160,057	4,438	708,105	6.27	0.63 (0.61-0.65)	< 0.001	0.92 (0.88-0.95)	< 0.001
	3-4 days/week	85,122	2,710	374,510	7.24	0.73 (0.70-0.76)	< 0.001	0.85 (0.81-0.88)	< 0.001
	≥5 days/week	52,922	2,105	221,409	9.51	0.96 (0.91-1.00)	0.08	0.84 (0.80-0.88)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S11. Risks of major adverse cardiovascular events according to the frequency of moderate-to-vigorous physical activity in each study group within subjects within female subjects.

MetS status	Frequency of MV-PA	Number of persons	Number of MACE	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	909,789	5,420	3,848,323	1.41	Reference		Reference	
	1-2 days/week	562,840	1,957	2,422,327	0.81	0.57 (0.54-0.60)	< 0.001	0.92 (0.87-0.97)	0.001
	3-4 days/week	298,833	1,233	1,253,084	0.98	0.70 (0.66-0.74)	< 0.001	0.84 (0.79-0.90)	< 0.001
	≥5 days/week	167,315	909	689,367	1.32	0.94 (0.87-1.00)	0.07	0.85 (0.8-0.92)	< 0.001
MetS-recovery	0 days/week	62,229	1,129	251,140	4.50	Reference		Reference	
	1-2 days/week	25,684	297	106,833	2.78	0.62 (0.54-0.70)	< 0.001	0.94 (0.83-1.07)	0.37
	3-4 days/week	17,660	195	71,272	2.74	0.61 (0.52-0.71)	< 0.001	0.85 (0.73-0.99)	0.04
	≥5 days/week	12,887	173	51,373	3.37	0.75 (0.64-0.88)	< 0.001	0.86 (0.73-1.01)	0.07
MetS-developed	0 days/week	76,378	1,826	296,799	6.15	Reference		Reference	
	1-2 days/week	27,615	426	109,805	3.88	0.63 (0.57-0.70)	< 0.001	0.91 (0.82-1.02)	0.09
	3-4 days/week	19,731	299	76,365	3.92	0.64 (0.56-0.72)	< 0.001	0.83 (0.73-0.93)	0.002
	≥5 days/week	14,834	265	56,968	4.65	0.76 (0.66-0.86)	< 0.001	0.86 (0.76-0.98)	0.03
MetS-chronic	0 days/week	223,458	8,010	858,308	9.33	Reference		Reference	
	1-2 days/week	65,467	1,658	257,555	6.44	0.69 (0.65-0.73)	< 0.001	0.92 (0.87-0.97)	0.002
	3-4 days/week	51,611	1,157	197,775	5.85	0.63 (0.59-0.67)	< 0.001	0.78 (0.73-0.83)	< 0.001
	≥5 days/week	42,747	1,114	163,195	6.83	0.73 (0.69-0.78)	< 0.001	0.83 (0.78-0.89)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S12. Risks of all-cause mortality according to the frequency of moderate-to-vigorous physical activity in each study group within subjects within male subjects.

MetS status	Frequency of MV-PA	Number of persons	Number of deaths	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	930,237	12,215	4,154,926	2.94	Reference		Reference	
	1-2 days/week	968,312	5,531	4,470,415	1.24	0.42 (0.41-0.43)	< 0.001	0.80 (0.78-0.83)	< 0.001
	3-4 days/week	457,437	3,424	2,122,554	1.61	0.55 (0.53-0.57)	< 0.001	0.78 (0.75-0.81)	< 0.001
	≥5 days/week	252,775	2,970	1,141,840	2.60	0.88 (0.85-0.92)	< 0.001	0.81 (0.78-0.84)	< 0.001
MetS-recovery	0 days/week	82,818	1,711	363,733	4.70	Reference		Reference	
	1-2 days/week	79,227	646	363,399	1.78	0.38 (0.35-0.41)	< 0.001	0.73 (0.66-0.8)	< 0.001
	3-4 days/week	42,056	442	192,758	2.29	0.49 (0.44-0.54)	< 0.001	0.72 (0.65-0.8)	< 0.001
	≥5 days/week	25,752	418	113,520	3.68	0.78 (0.70-0.87)	< 0.001	0.76 (0.68-0.85)	< 0.001
MetS-developed	0 days/week	80,162	1,661	342,702	4.85	Reference		Reference	
	1-2 days/week	73,896	765	329,933	2.32	0.48 (0.44-0.52)	< 0.001	0.87 (0.79-0.95)	0.002
	3-4 days/week	35,099	445	156,708	2.84	0.59 (0.53-0.65)	< 0.001	0.73 (0.65-0.81)	< 0.001
	≥5 days/week	20,448	365	87,821	4.16	0.86 (0.77-0.96)	0.008	0.69 (0.62-0.78)	< 0.001
MetS-chronic	0 days/week	182,679	4,378	781,635	5.60	Reference		Reference	
	1-2 days/week	160,057	1,811	717,283	2.52	0.45 (0.43-0.48)	< 0.001	0.78 (0.74-0.83)	< 0.001
	3-4 days/week	85,122	1,284	380,113	3.38	0.60 (0.57-0.64)	< 0.001	0.73 (0.69-0.78)	< 0.001
	≥5 days/week	52,922	1,163	225,588	5.16	0.92 (0.86-0.98)	0.012	0.77 (0.72-0.83)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S13. Risks of all-cause mortality according to the frequency of moderate-to-vigorous physical activity in each study group within subjects within female subjects.

MetS status	Frequency of MV-PA	Number of persons	Number of deaths	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MetS-free	0 days/week	909,789	3,406	3,857,951	0.88	Reference		Reference	
	1-2 days/week	562,840	1,202	2,425,889	0.50	0.56 (0.53-0.60)	< 0.001	0.9 (0.84-0.96)	0.003
	3-4 days/week	298,833	721	1,255,274	0.57	0.65 (0.60-0.70)	< 0.001	0.82 (0.76-0.89)	< 0.001
	≥5 days/week	167,315	589	690,973	0.85	0.97 (0.88-1.05)	0.43	0.92 (0.84-1.00)	0.06
MetS-recovery	0 days/week	62,229	665	253,094	2.63	Reference		Reference	
	1-2 days/week	25,684	114	107,384	1.06	0.40 (0.33-0.49)	< 0.001	0.68 (0.56-0.83)	< 0.001
	3-4 days/week	17,660	84	71,642	1.17	0.45 (0.36-0.56)	< 0.001	0.72 (0.58-0.91)	0.006
	≥5 days/week	12,887	71	51,665	1.37	0.52 (0.41-0.67)	< 0.001	0.69 (0.54-0.88)	0.003
MetS-developed	0 days/week	76,378	806	300,048	2.69	Reference		Reference	
	1-2 days/week	27,615	168	110,590	1.52	0.57 (0.48-0.67)	< 0.001	0.91 (0.77-1.08)	0.28
	3-4 days/week	19,731	105	76,885	1.37	0.51 (0.41-0.62)	< 0.001	0.74 (0.60-0.90)	0.003
	≥5 days/week	14,834	107	57,460	1.86	0.69 (0.57-0.85)	< 0.001	0.85 (0.69-1.04)	0.11
MetS-chronic	0 days/week	223,458	3,223	872,563	3.69	Reference		Reference	
	1-2 days/week	65,467	557	260,695	2.14	0.58 (0.53-0.63)	< 0.001	0.84 (0.77-0.92)	< 0.001
	3-4 days/week	51,611	379	199,884	1.90	0.51 (0.46-0.57)	< 0.001	0.72 (0.65-0.80)	< 0.001
	≥5 days/week	42,747	414	165,234	2.51	0.68 (0.61-0.75)	< 0.001	0.84 (0.76-0.93)	< 0.001

MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S14. Characteristics of those with undetermined MetS status who were not included in the main analysis.

Variables	Undetermined MetS status (N = 1,297,589)
Clinical and demographic characteristics at S3	
Age (years)	51.0 ± 12.8
Sex (male)	829,324 (63.9)
Height (cm)	164.9 ± 9.6
Weight (kg)	68.7 ± 12.2
BMI (kg/m^2)	25.1 ± 3.0
Low-income status*	248,855 (19.2)
CCI (score)	0.9 ± 1.2
Hemoglobin (g/dL)	14.4 ± 1.6
AST (IU/L)	27.5 ± 22.6
ALT (IU/L)	29.8 ± 26.9
Cr (mg/dL)	0.89 ± 0.19
eGFR (mL/min/1.73 m^2)	90.1 ± 31.8
Self-reported lifestyle (n (%))	
Moderate-to-vigorous activity	
None	602,875 (46.5)
1-2 days/wk	380,888 (29.4)
3-4 days/wk	189,579 (14.6)
≥ 5 days/wk	124,247 (9.6)
Smoking	
Nonsmoker	684,976 (52.8)
Ex-smoker	211,688 (16.3)
Current light-to-moderate smoker	202,816 (15.6)
Current heavy smoker	198,109 (15.3)
Alcohol	
No alcohol intake	608,088(46.9)
Moderate consumption	58,720(4.5)
Heavy consumption	630,781(48.6)
Parameters of MetS	
Waist circumference (cm)	84.5 ± 7.8
Systolic BP (mmHg)	126.9 ± 13.4
Diastolic BP (mmHg)	79.2 ± 9.4
Glucose (mg/dL)	101.8 ± 22.4
Triglycerides (mg/dL)	173.2 ± 120.7
HDL cholesterol (mg/dL)	50.7 ± 14.5
Baseline N of MetS components (n (%))	
0	41,098 (3.2)
1	167,341 (12.9)
2	363,965 (28.1)
3	536,723 (41.4)
4	163,997 (12.6)
5	24,465 (1.9)

AST = aspartate aminotransferase, ALT = alanine aminotransferase, BMI = body mass index, BP = blood pressure, CCI = Charlson Comorbidity Index, Cr = creatinine, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, MetS = metabolic syndrome
There were no missing values in the table.

Table S15. Risks of major adverse cardiovascular events and all-cause mortality according to the frequency of moderate-to-vigorous physical activity in each study group within those who were excluded due to their undetermined MetS status

Outcome	Frequency of MV-PA	Number of persons	Number of outcomes	Follow-up (person-years)	Incidence rate (/1000 person-years)	Unadjusted model		Multivariable model	
						IRR (95% CI)	P	Adjusted IRR (95% CI)	P
MACE	0 days/week	561,977	13,450	2,328,970	5.78	Reference		Reference	
	1-2 days/week	393,223	5,814	1,726,226	3.37	0.58 (0.57-0.60)	< 0.001	0.89 (0.86-0.92)	< 0.001
	3-4 days/week	210,454	3,741	909,856	4.11	0.71 (0.69-0.74)	< 0.001	0.88 (0.84-0.91)	< 0.001
	≥5 days/week	131,935	2,996	550,290	5.44	0.94 (0.91-0.98)	0.004	0.87 (0.84-0.91)	< 0.001
All-cause mortality	0 days/week	561,977	8,642	2,353,895	3.67	Reference		Reference	
	1-2 days/week	393,223	3,190	1,737,700	1.84	0.50 (0.48-0.52)	< 0.001	0.85 (0.81-0.88)	< 0.001
	3-4 days/week	210,454	2,026	917,287	2.21	0.60 (0.57-0.63)	< 0.001	0.78 (0.75-0.82)	< 0.001
	≥5 days/week	131,935	1,788	555,994	3.22	0.88 (0.83-0.92)	< 0.001	0.78 (0.74-0.82)	< 0.001

MACE = major adverse cardiovascular event, MetS = metabolic syndrome, MV-PA, moderate-to-vigorous physical activity, IRR = incidence rate ratio, CI = confidence interval

Multivariable model was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL), aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low-income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), Charlson Comorbidity Index score, place of residence (urban or rural), and the number of MetS components at the baseline health screening.

Table S16. Risks of major adverse cardiovascular events according to frequencies of moderate-to-vigorous physical activity in those with consistently free or chronically present metabolic syndrome component.

Subgroups and exposure	Number of persons	Number of MACE	Follow-up (person-years)	Incidence rate (/1000 person-years)	Model 1. Unadjusted model		Model 2. Age-sex adjusted model		[a] Model 3. Baseline severity of MetS (number of MetS components) and other lifestyle variables (smoking, alcohol) adjusted	
					Adjusted IRR (95% CI)	P	Adjusted IRR (95% CI)	P	Adjusted IRR (95% CI)	P
Central obesity-free										
0 days/week	1,653,227	19,084	7,199,247	2.65	Reference		Reference		Reference	
1-2 days/week	1,407,541	10,100	6,355,181	1.59	0.6 (0.59-0.61)	< 0.001	0.9 (0.88-0.92)	< 0.001	0.93 (0.91-0.95)	< 0.001
3-4 days/week	696,957	6,025	3,120,635	1.93	0.73 (0.71-0.75)	< 0.001	0.83 (0.8-0.85)	< 0.001	0.86 (0.83-0.88)	< 0.001
≥ 5 days/week	391,800	4,813	1,706,720	2.82	1.06 (1.03-1.1)	< 0.001	0.84 (0.81-0.87)	< 0.001	0.86 (0.83-0.89)	< 0.001
Central obesity-chronic										
0 days/week	373,002	10,934	1,501,075	7.28						
1-2 days/week	204,696	3,830	877,334	4.37	0.6 (0.58-0.62)	< 0.001	0.91 (0.88-0.94)	< 0.001	0.94 (0.91-0.98)	0.003
3-4 days/week	114,223	2,377	477,967	4.97	0.68 (0.65-0.71)	< 0.001	0.84 (0.8-0.88)	< 0.001	0.88 (0.84-0.92)	< 0.001
≥ 5 days/week	75,812	1,921	306,723	6.26	0.86 (0.82-0.9)	< 0.001	0.83 (0.79-0.87)	< 0.001	0.86 (0.82-0.91)	< 0.001
High blood pressure-free										
0 days/week	1,050,775	5,603	4,562,450	1.23	Reference		Reference		Reference	
1-2 days/week	867,072	3,234	3,871,018	0.84	0.68 (0.65-0.71)	< 0.001	0.87 (0.83-0.91)	< 0.001	0.9 (0.86-0.94)	< 0.001
3-4 days/week	406,945	1,712	1,797,510	0.95	0.78 (0.73-0.82)	< 0.001	0.79 (0.75-0.83)	< 0.001	0.84 (0.8-0.89)	< 0.001
≥ 5 days/week	212,349	1,179	920,271	1.28	1.04 (0.98-1.11)	0.187	0.81 (0.76-0.86)	< 0.001	0.86 (0.81-0.92)	< 0.001
High blood pressure-chronic										
0 days/week	635,759	22,936	2,589,510	8.86	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001
1-2 days/week	391,097	9,014	1,707,914	5.28	0.6 (0.58-0.61)	< 0.001	0.88 (0.86-0.9)	< 0.001	0.92 (0.9-0.95)	< 0.001
3-4 days/week	242,882	5,925	1,042,980	5.68	0.64 (0.62-0.66)	< 0.001	0.79 (0.77-0.81)	< 0.001	0.84 (0.82-0.87)	< 0.001
≥ 5 days/week	169,629	5,151	697,897	7.38	0.83 (0.81-0.86)	< 0.001	0.8 (0.78-0.83)	< 0.001	0.85 (0.83-0.88)	< 0.001
Impaired glucose tolerance-free										
0 days/week	1,366,571	13,549	5,908,689	2.29	Reference		Reference		Reference	
1-2 days/week	1,109,805	6,629	4,977,648	1.33	0.58 (0.56-0.6)	< 0.001	0.9 (0.87-0.93)	< 0.001	0.94 (0.91-0.96)	< 0.001
3-4 days/week	541,418	3,831	2,401,527	1.60	0.7 (0.67-0.72)	< 0.001	0.83 (0.8-0.86)	< 0.001	0.89 (0.86-0.92)	< 0.001
≥ 5 days/week	294,940	2,800	1,276,663	2.19	0.96 (0.92-1)	0.032	0.81 (0.78-0.84)	< 0.001	0.88 (0.84-0.91)	< 0.001
Impaired glucose tolerance-chronic										
0 days/week	322,541	12,083	1,302,705	9.28	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001
1-2 days/week	201,676	5,061	870,880	5.81	0.63 (0.61-0.65)	< 0.001	0.89 (0.86-0.92)	< 0.001	0.94 (0.91-0.98)	< 0.001
3-4 days/week	126,855	3,380	539,761	6.26	0.68 (0.65-0.7)	< 0.001	0.8 (0.77-0.83)	< 0.001	0.87 (0.83-0.9)	< 0.001
≥ 5 days/week	91,049	2,948	371,119	7.94	0.86 (0.82-0.89)	< 0.001	0.8 (0.77-0.83)	< 0.001	0.86 (0.83-0.9)	< 0.001
High Tg-free										
0 days/week	1,395,443	13,959	5,998,236	2.33	Reference		Reference		Reference	
1-2 days/week	1,100,029	6,374	4,898,158	1.30	0.56 (0.54-0.58)	< 0.001	0.9 (0.87-0.93)	< 0.001	0.95 (0.92-0.98)	< 0.001
3-4 days/week	567,617	3,947	2,500,091	1.58	0.68 (0.65-0.7)	< 0.001	0.81 (0.79-0.84)	< 0.001	0.86 (0.83-0.89)	< 0.001
≥ 5 days/week	328,192	3,331	1,409,925	2.36	1.02 (0.98-1.05)	0.434	0.83 (0.8-0.86)	< 0.001	0.87 (0.84-0.9)	< 0.001
High Tg-chronic										
0 days/week	427,767	12,962	1,777,758	7.29	Reference		Reference		Reference	
1-2 days/week	311,342	6,117	1,380,051	4.43	0.61 (0.59-0.63)	< 0.001	0.89 (0.86-0.92)	< 0.001	0.94 (0.91-0.97)	< 0.001
3-4 days/week	160,377	3,572	696,959	5.13	0.7 (0.68-0.73)	< 0.001	0.81 (0.78-0.84)	< 0.001	0.86 (0.83-0.9)	< 0.001
≥ 5 days/week	97,219	2,709	404,610	6.70	0.92 (0.88-0.96)	< 0.001	0.81 (0.78-0.85)	< 0.001	0.85 (0.82-0.89)	< 0.001
Low HDL-free										
0 days/week	1,556,877	17,063	6,767,666	2.52	Reference		Reference		Reference	
1-2 days/week	1,347,104	9,063	6,070,028	1.49	0.59 (0.58-0.61)	< 0.001	0.9 (0.88-0.92)	< 0.001	0.94 (0.92-0.97)	< 0.001
3-4 days/week	668,382	5,390	2,991,964	1.80	0.71 (0.69-0.74)	< 0.001	0.83 (0.81-0.86)	< 0.001	0.89 (0.87-0.92)	< 0.001
≥ 5 days/week	374,961	4,189	1,634,768	2.56	1.02 (0.98-1.05)	0.347	0.83 (0.8-0.86)	< 0.001	0.88 (0.85-0.91)	< 0.001
Low HDL-chronic										
0 days/week	296,655	9,335	1,195,777	7.81	Reference		Reference		Reference	
1-2 days/week	157,794	3,406	676,315	5.04	0.64 (0.62-0.67)	< 0.001	0.88 (0.84-0.92)	< 0.001	0.92 (0.89-0.96)	< 0.001
3-4 days/week	98,268	2,251	408,466	5.51	0.71 (0.67-0.74)	< 0.001	0.78 (0.75-0.82)	< 0.001	0.83 (0.79-0.87)	< 0.001
≥ 5 days/week	67,719	1,904	272,183	7.00	0.9 (0.85-0.94)	< 0.001	0.8 (0.76-0.84)	< 0.001	0.84 (0.8-0.88)	< 0.001

MetS = metabolic syndrome, IRR = incidence rate ratio, CI = confidence interval, Tg = triglyceride, HDL = high-density lipoprotein cholesterol

[a] Model 3 was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), and Charlson Comorbidity Index, place of residences (urban or rural) and the number of MetS components at the baseline (S1) health screening, and the other lifestyle variables (smoking; none, previous, current and alcohol consumption; none, moderate, heavy)

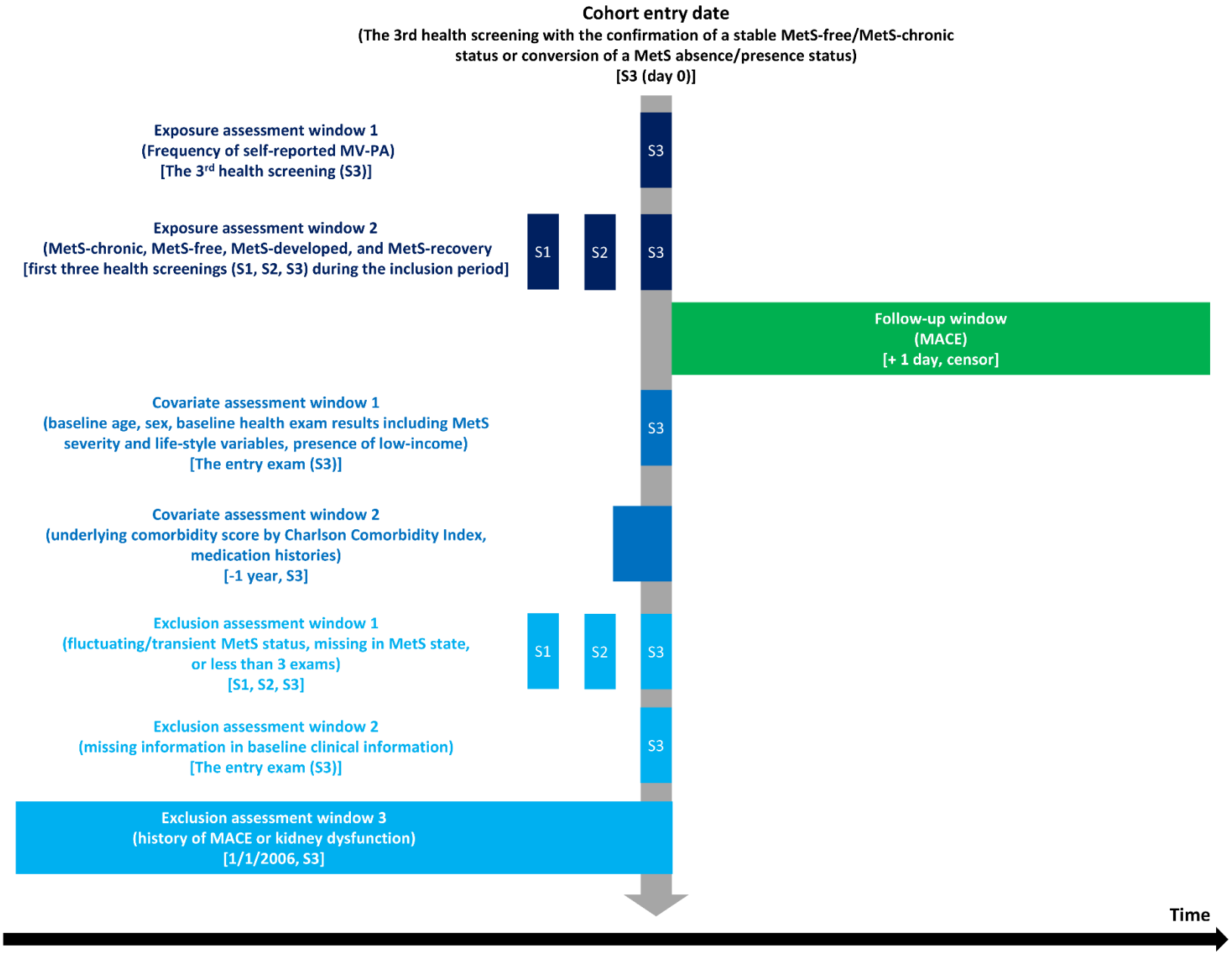
Table S17. Risks of all-cause mortality according to frequencies of moderate-to-vigorous physical activity in those with consistently free or chronically present metabolic syndrome component.

Subgroups and exposure	Number of persons	Number of deaths	Follow-up (person-years)	Incidence rate (/1000 person-years)	Model 1. Unadjusted model		Model 2. Age-sex adjusted model		[a] Model 3. Baseline severity of MetS (number of MetS components) and other lifestyle variables (smoking, alcohol) adjusted	
					Adjusted IRR (95% CI)	P	Adjusted IRR (95% CI)	P	Adjusted IRR (95% CI)	P
Central obesity-free										
0 days/week	1,653,227	16,751	7,235,006	2.32	Reference		Reference		Reference	
1-2 days/week	1,407,541	7,126	6,375,448	1.12	0.48 (0.47-0.5)	< 0.001	0.75 (0.73-0.77)	< 0.001	0.85 (0.82-0.87)	< 0.001
3-4 days/week	696,957	4,485	3,132,640	1.43	0.62 (0.6-0.64)	< 0.001	0.71 (0.69-0.74)	< 0.001	0.83 (0.81-0.86)	< 0.001
≥ 5 days/week	391,800	3,942	1,715,988	2.30	0.99 (0.96-1.03)	0.658	0.77 (0.74-0.8)	< 0.001	0.87 (0.84-0.9)	< 0.001
Central obesity-chronic										
0 days/week	373,002	5,166	1,521,190	3.40	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001
1-2 days/week	204,696	1,543	884,959	1.74	0.51 (0.49-0.54)	< 0.001	0.8 (0.75-0.85)	< 0.001	0.85 (0.8-0.9)	< 0.001
3-4 days/week	114,223	978	482,688	2.03	0.6 (0.56-0.64)	< 0.001	0.73 (0.68-0.78)	< 0.001	0.77 (0.72-0.83)	< 0.001
≥ 5 days/week	75,812	904	310,321	2.91	0.86 (0.8-0.92)	< 0.001	0.78 (0.73-0.84)	< 0.001	0.81 (0.76-0.87)	< 0.001
High blood pressure-free										
0 days/week	1,050,775	4,776	4,572,913	1.04	Reference		Reference		Reference	
1-2 days/week	867,072	2,494	3,877,338	0.64	0.62 (0.59-0.65)	< 0.001	0.76 (0.73-0.8)	< 0.001	0.84 (0.8-0.88)	< 0.001
3-4 days/week	406,945	1,455	1,800,830	0.81	0.77 (0.73-0.82)	< 0.001	0.77 (0.73-0.82)	< 0.001	0.85 (0.8-0.91)	< 0.001
≥ 5 days/week	212,349	1,085	922,515	1.18	1.13 (1.05-1.2)	< 0.001	0.85 (0.79-0.91)	< 0.001	0.9 (0.84-0.96)	0.001
High blood pressure-chronic										
0 days/week	635,759	14,098	2,632,115	5.36	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001	1 (Ref.)	< 0.001
1-2 days/week	391,097	4,492	1,726,092	2.60	0.49 (0.47-0.5)	< 0.001	0.76 (0.74-0.79)	< 0.001	0.84 (0.81-0.87)	< 0.001
3-4 days/week	242,882	3,175	1,054,728	3.01	0.56 (0.54-0.58)	< 0.001	0.7 (0.68-0.73)	< 0.001	0.77 (0.74-0.8)	< 0.001
≥ 5 days/week	169,629	2,989	707,734	4.22	0.79 (0.76-0.82)	< 0.001	0.72 (0.69-0.75)	< 0.001	0.78 (0.75-0.81)	< 0.001
Impaired glucose tolerance-free										
0 days/week	1,366,571	9,699	5,933,883	1.63	Reference		Reference		Reference	
1-2 days/week	1,109,805	4,078	4,990,844	0.82	0.5 (0.48-0.52)	< 0.001	0.75 (0.72-0.78)	< 0.001	0.82 (0.79-0.85)	< 0.001
3-4 days/week	541,418	2,499	2,409,100	1.04	0.63 (0.61-0.66)	< 0.001	0.74 (0.7-0.77)	< 0.001	0.81 (0.78-0.85)	< 0.001
≥ 5 days/week	294,940	2,033	1,282,111	1.59	0.97 (0.92-1.02)	0.214	0.78 (0.75-0.82)	< 0.001	0.85 (0.81-0.89)	< 0.001
Impaired glucose tolerance-chronic										
0 days/week	322,541	7,525	1,325,296	5.68	Reference		Reference		Reference	
1-2 days/week	201,676	2,539	880,948	2.88	0.51 (0.49-0.53)	< 0.001	0.75 (0.71-0.78)	< 0.001	0.82 (0.79-0.86)	< 0.001
3-4 days/week	126,855	1,791	546,513	3.28	0.58 (0.55-0.61)	< 0.001	0.68 (0.65-0.72)	< 0.001	0.74 (0.71-0.78)	< 0.001
≥ 5 days/week	91,049	1,800	376,786	4.78	0.84 (0.8-0.89)	< 0.001	0.73 (0.7-0.77)	< 0.001	0.78 (0.74-0.82)	< 0.001
High Tg-free										
0 days/week	1,395,443	13,039	6,023,606	2.16	Reference		Reference		Reference	
1-2 days/week	1,100,029	5,050	4,910,424	1.03	0.48 (0.46-0.49)	< 0.001	0.76 (0.74-0.79)	< 0.001	0.84 (0.81-0.87)	< 0.001
3-4 days/week	567,617	3,310	2,507,661	1.32	0.61 (0.59-0.63)	< 0.001	0.72 (0.69-0.75)	< 0.001	0.82 (0.78-0.85)	< 0.001
≥ 5 days/week	328,192	3,034	1,416,202	2.14	0.99 (0.95-1.03)	0.607	0.77 (0.74-0.8)	< 0.001	0.85 (0.82-0.89)	< 0.001
High Tg-chronic										
0 days/week	427,767	6,133	1,802,514	3.40	Reference		Reference		Reference	
1-2 days/week	311,342	2,446	1,392,563	1.76	0.52 (0.49-0.54)	< 0.001	0.79 (0.75-0.83)	< 0.001	0.85 (0.81-0.89)	< 0.001
3-4 days/week	160,377	1,531	704,123	2.17	0.64 (0.6-0.68)	< 0.001	0.74 (0.7-0.79)	< 0.001	0.79 (0.74-0.83)	< 0.001
≥ 5 days/week	97,219	1,309	409,983	3.19	0.94 (0.88-1)	0.037	0.79 (0.74-0.83)	< 0.001	0.83 (0.78-0.88)	< 0.001
Low HDL-free										
0 days/week	1,556,877	14,883	6,799,437	2.19	Reference		Reference		Reference	
1-2 days/week	1,347,104	6,613	6,087,912	1.09	0.5 (0.48-0.51)	< 0.001	0.77 (0.75-0.79)	< 0.001	0.85 (0.82-0.87)	< 0.001
3-4 days/week	668,382	4,097	3,002,588	1.36	0.62 (0.6-0.65)	< 0.001	0.73 (0.71-0.76)	< 0.001	0.82 (0.8-0.85)	< 0.001
≥ 5 days/week	374,961	3,578	1,642,865	2.18	0.99 (0.96-1.03)	0.788	0.79 (0.76-0.82)	< 0.001	0.86 (0.83-0.9)	< 0.001
Low HDL-chronic										
0 days/week	296,655	4,459	1,213,168	3.68	Reference		Reference		Reference	
1-2 days/week	157,794	1,318	683,112	1.93	0.52 (0.49-0.56)	< 0.001	0.77 (0.72-0.82)	< 0.001	0.83 (0.78-0.89)	< 0.001
3-4 days/week	98,268	966	412,846	2.34	0.64 (0.59-0.68)	< 0.001	0.73 (0.68-0.78)	< 0.001	0.78 (0.73-0.84)	< 0.001
≥ 5 days/week	67,719	903	275,775	3.27	0.89 (0.83-0.96)	0.002	0.76 (0.71-0.82)	< 0.001	0.8 (0.75-0.86)	< 0.001

MetS = metabolic syndrome, IRR = incidence rate ratio, CI = confidence interval, Tg = triglyceride, HDL = high-density lipoprotein cholesterol

[a] Model 3 was adjusted for age, sex, baseline eGFR (continuous, mL/min/1.73 m^2), alanine aminotransferase (continuous, IU/mL aspartate aminotransferase (continuous, IU/mL), hemoglobin (continuous, g/dL), low income status (the lowest quartile in the nation), body mass index (continuous, kg/m^2), and Charlson Comorbidity Index, place of residences (urban or rural) and the number of MetS components at the baseline (S1) health screening, and the other lifestyle variables (smoking; none, previous, current and alcohol consumption; none, moderate, heavy)

Figure S1. Graphical description of the study population.



MetS = metabolic syndrome, MV-PA = moderate-to vigorous physical activity, MACE = major adverse cardiovascular events

Figure S2. English version questionnaire used in general health screenings by the National Health Insurance Service of Korea.

[Annex No. 1] <Front>

National Screening Program

☐ **Regular checkup** ☐ **Life cycle-based checkup**

※ Answers must be provided for all questions so the information will be reported correctly.

First Name		Residential ID No.		Telephone	Home	
Given Name					Mobile phone	
Current address					Zip code	-
					E-mail	

※ These are questions about your medical history.

※ Please answer the following questions about your present condition by ticking the appropriate box.

1. Have you ever been diagnosed by a doctor with any of the following diseases (Box a) or are you currently taking any medication (Box b)?

Disease	Brain stroke / paralysis	Heart disease (cardiac infarction / angina)	High blood pressure	Diabetes	Dyslipidemia	Tuberculosis	Others (including cancer)
a							
b							

2. Has anyone in your family died from or gotten any of the following diseases?

Disease	Brain stroke / paralysis	Heart disease (cardiac infarction / angina)	High blood pressure	Diabetes	Others (including cancer)
Yes					

3. Are you a Hepatitis B virus antigen carrier? ① Yes ② No ③ No idea

※ These are questions about smoking.

4. Please answer the following questions about your present condition by ticking the appropriate box.

4-1. Have you ever smoked over 5 packs of tobacco (100 cigarettes) in your life?

① No, I never smoked. (☞ Go to Question 5) ② Yes, I used to smoke but I stopped. (☞ Go to Question 4-2)

③ Yes, I'm still smoking (☞ Go to Question 4-3)

4-2. If you used to smoke but stopped, please answer the following.

For how many years had you smoked?	Total_____years
How many cigarettes in a typical day did you smoke before you stopped?	_____cigarettes

4-3. If you are still smoking, please answer the following.

How long have you been smoking?	Total_____years
How many cigarettes on average do you smoke on a regular day?	_____cigarettes

※ These are questions about drinking.

5. Please answer the following questions about your current drinking habit by ticking the appropriate box.

5-1. How many times a week do you drink alcohol?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

5-2. When you drink, how much do you usually drink on a regular day? (glass(es))

(※ No matter what kind of liquor it may be, each glass will be considered as 1 glass. However, 1 can of beer (355 cc) is equal to 1.6 glasses of beer.)

[Annex No. 1] <Back>

※ These are questions about exercising.

6. These are questions about your physical activity for the last week. Please answer the following questions by ticking the appropriate box.

6-1. During the last week, how many days did you exercise vigorously for over 20 minutes until you were almost out of breath? (example: running, aerobics, high-speed cycling, mountain hiking, etc.)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

6-2. During the last week, how many days did you exercise in a moderate level for more than 30 minutes until you had to breathe a little faster than usual? (example: fast walking, tennis, bicycle riding, cleaning, etc.) ※ Except the relevant answer from 6-1

☐ 0 ☐ 1 ☐ 2 ☐3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

6-3. During the last week, how many days did you walk for a total of 30 minutes or more in a day, including separate 10-minute walks? (example: light exercise, walk for work or for leisure, etc.)

※ Please exclude exercises you answered in 6-1 and 6-2

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

※ **These are questions about cognitive functions. (Only answer if you are 66, 70, or 74 years old.)** (If a family member accompanied you, please let him/her answer the questions. If not, answer the following questions by yourself.)

7. Please answer the following questions about your current cognitive condition compared to last year by ticking the appropriate box.

7-1. Compared to friends or other people, your memory is worse than others.

① No ② Occasionally ③ Yes

7-2. Your memory is worse compared to last year.

① No ② Occasionally ③ Yes

7-3. You experience problems related to your memory when handling important matters.

① No ② Occasionally ③ Yes

7-4. Has anyone noticed that you have a short memory?

① No ② Occasionally ③ Yes

7-5. Do you experience difficulties in performing daily chores that you used to do well before?

① No ② Occasionally ③ Yes

※ Emotional status (Only answer if you are 40 years old.)

8. Please identify how many times you experienced the following during the last week by ticking the appropriate box.

During the last week, I	Hardly ever (less than 1 day)	Not too often (couple of days)	Sometimes (more than 3 days)	Always (over 5 days)
8-1. Was annoyed and bothered by things that were not there before.				
8-2. Did not want to eat and even lost appetite.				
8-3. Felt sad even when someone tried to help me out.				
8-4. Felt depressed.				

※ Please complete this form with Annex No. 2 only 66 years old.

210 ㎜ × 297 ㎜ [백상지 80 g/㎡]