Annals of Internal Medicine ORIGINAL RESEARCH

Altered Risk for Cardiovascular Events With Changes in the Metabolic Syndrome Status

A Nationwide Population-Based Study of Approximately 10 Million Persons

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Background: Population-scale evidence for the association between dynamic changes in metabolic syndrome (MetS) status and alterations in the risk for major adverse cardiovascular events (MACE) is lacking.

Objective: To investigate whether recovery from or development of MetS in a population is associated with an altered risk for MACE.

Design: Nationwide cohort study.

Setting: An analysis based on the National Health Insurance Database of Korea.

Participants: A total of 27 161 051 persons who received national health screenings from 2009 to 2014 were screened. Those with a history of MACE were excluded. We determined the MetS status of 9 553 042 persons using the following harmonizing criteria: MetS-chronic (n = 1 486 485), MetS-developed (n = 587 088), MetS-recovery (n = 538 806), and MetS-free (n = 6 940 663).

Measurements: The outcome was the occurrence of MACE, including acute myocardial infarction, revascularization, and acute ischemic stroke, identified from the claims database. The incidence rate ratios (IRRs) were calculated with adjustments for body mass index, comorbidity scores, previous metabolic variables, and other clinical or demographic variables.

Results: At a median follow-up of 3.54 years, the MetS-recovery group (incidence rate, 4.55 per 1000 person-years) had a significantly lower MACE risk (adjusted IRR, 0.85 [95% CI, 0.83 to 0.87]) than that of the MetS-chronic group (incidence rate, 8.52 per 1000 person-years). The MetS-developed group (incidence rate, 6.05 per 1000 person-years) had a significantly higher MACE risk (adjusted IRR, 1.36 [CI, 1.33 to 1.39]) than that of the MetS-free group (incidence rate, 1.92 per 1000 person-years). Among the MetS components, change in hypertension was associated with the largest difference in MACE risk.

Limitation: Limited assessment of mortality and short follow-up.

Conclusion: Recovery from MetS was significantly associated with decreased risk for MACE, whereas development of MetS was associated with increased risk.

Primary Funding Source: Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea.

Ann Intern Med. doi:10.7326/M19-0563 **Annals.org**
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This article was published at Annals.org on 26 November 2019.

Metabolic syndrome (MetS) increases the risk for major adverse cardiovascular events (MACE), a leading cause of death in adults worldwide (1–5). Several medical resources are invested in managing MetS components, which include central obesity, dyslipidemia, glucose intolerance, and hypertension (6–9). However, the medical burden of MetS and consequential MACE is projected to increase as obesity-related health problems grow worldwide (9).

Management of each MetS component has proven to be effective in reducing the risk for MACE (10–13). In addition, population-based studies have found that MetS is an important predictor of MACE (2–4, 14). However, few large-scale studies that explore whether recovery from or development of MetS is associated with an altered risk for MACE have been done, although MetS status has been reported to change dynamically (15–17). Identifying the risk for MACE in persons who develop or recover from MetS would be essential evidence in support of public health policies aiming to reduce the burden of MetS (17–21). Furthermore, comparing the different risks for MACE associated with each MetS component would reveal a potential approach for decreasing MetS-related cardiovascular events.

In this study, we investigated the association between dynamic MetS status and MACE risk. We included approximately 10 million persons who showed alterations in or maintenance of MetS status during the course of serial health checkups. We hypothesized that persons with an altered MetS status or alterations in each MetS component would have an altered risk for MACE.

METHODS

The Institutional Review Board of Seoul National University Hospital (E-1801-027-913) approved the study. They waived the requirement for informed consent because anonymous raw data were obtained from the National Health Insurance Service of Korea. The study was done in accordance with the Declaration of Helsinki.

See also:

Summary for Patients

The National Health Insurance Database and National Health Screening in Korea

The National Health Insurance Database of Korea, a public resource of data from the entire South Korean population, includes information on insured medical services, health screenings, and sociodemographic variables (22, 23). We used the health screening data to identify the MetS status of the persons studied and the diagnostic codes and relevant claims information to identify the outcomes (24).

A free general health screening is provided by the National Health Insurance Service every year for nonoffice workers and every 2 years for office workers or nonworkplace subscribers. Dependent subscribers who are older than 40 years also receive the examination every 2 years. Since 2009, the total examination rate for general health screenings among the approximately 15 million target population was approximately 70%.

Study Population

The graphical description of the time windows used to determine inclusion or exclusion of participants, covariates, and follow-up durations is shown in Appendix Figure 1 (available at Annals.org) (25). We screened adults (aged ≥20 years) who received general health screenings from the National Health Insurance Service from 2009 to 2014 in Korea. We included persons with identifiable MetS status at 3 or more health examinations during the inclusion period, and we determined the dynamic MetS status of the study population during the first 3 health screenings (S1, S2, and S3). To secure data availability, we excluded persons who had fewer than 3 health examinations and those who had missing information needed to identify their MetS status or baseline laboratory results. As eligibility criteria, we also excluded persons who had a transient change in MetS status and those who exhibited changes at their third examination (S3), because further confirmation for consistency during the inclusion health screenings (S1, S2, and S3) was not available for these persons (Appendix Figure 2, available at Annals.org). In addition, we excluded persons who had a history of MACE before follow-up initiation (1 day after the third examination) and those with underlying kidney function impairment (baseline estimated glomerular filtration rate of <60 mL/min/1.73 m^2; calculated using the Modification of Diet in Renal Disease Study equation, a chronic kidney disease diagnostic code, or a history of renal replacement therapy). Using these eligibility criteria, we aimed to include persons who maintained or exhibited persistent changes in their MetS status through 1 additional health examination without underlying MACE or significant kidney function impairment.

Data Collection

The following baseline characteristics were collected at the third screening (S3): age; sex; body mass index (BMI); waist circumference; systolic and diastolic blood pressure; estimated glomerular filtration rate calculated from serum creatinine value; and fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglyceride, alanine aminotransferase, aspartate aminotransferase, and hemoglobin levels. Persons 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 comorbid conditions in the included persons (26). Self-reported lifestyle variables were recorded as follows: days of moderate-to-vigorous physical activity for more than 20 to 30 minutes per week (0, 1 to 2, 3 to 4, and ≥5 days per week), smoking history, alcohol history (none, moderate consumption [≤2 standard drinks for men and ≤1 standard drink for women per single drinking session], and heavy consumption [more than moderate]) (27).

Definition of MetS

MetS status was identified by using the harmonizing criteria in the first 3 health screenings (S1, S2, and S3) (28). It was confirmed when 3 or more of the following components were present: increased waist circumference (≥90 cm for Asian men and ≥80 cm for Asian women); elevated triglyceride level (≥50 mg/dL) or use of a relevant drug; reduced high-density lipoprotein cholesterol level (<40 mg/dL for men and 50 mg/dL for women) or use of a relevant drug; elevated blood pressure (systolic ≥130 mm Hg and/or diastolic ≥80 mm Hg) or use of an antihypertensive medication; and elevated fasting glucose level (≥100 mg/dL) or use of an antidiabetic drug.

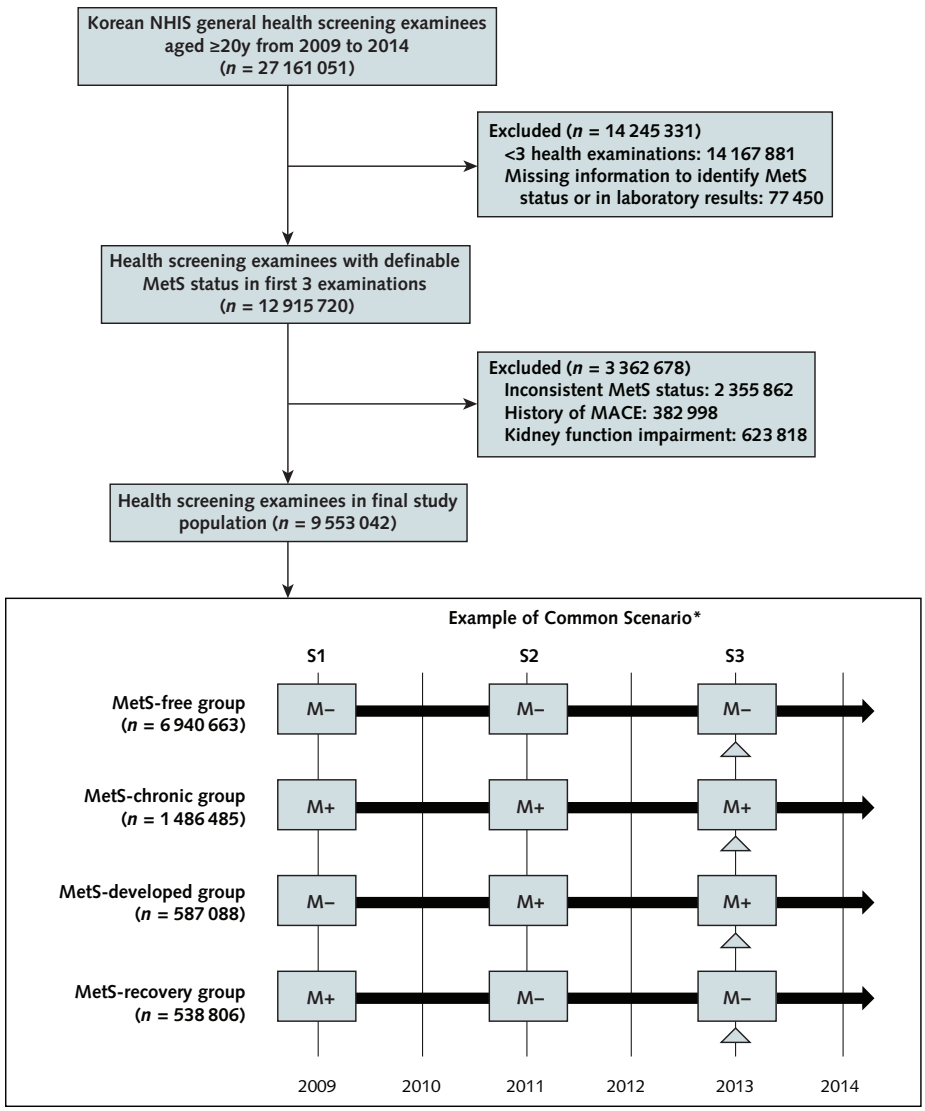
Study Groups

On the basis of our exclusion criteria, persons in the study population could have a status of stable MetS absence or presence or a change in their MetS absence or presence status from S2 and their MetS status maintained until S3. Study participants were divided into 4 groups according to MetS status (Figure 1): MetS-free (persons who were consistently free from MetS during the first 3 health examinations), MetS-chronic (those who had MetS throughout the 3 health examinations), MetS-developed (those with newly developed MetS [absence of MetS at S1 but presence of MetS at S2 and S3]), and MetS-recovery (those who recovered from preexisting MetS [presence of MetS at S1 but absence of MetS at S2 and S3]).

Study Outcomes

The study outcome was MACE, including acute myocardial infarction, revascularization, and acute ischemic stroke. Acute myocardial infarction was defined by International Classification of Diseases, 10th Revision, diagnostic code I21 or I22 during admission. Revascularization was defined by a claim history of a cardiovascular revascularization procedure. Acute ischemic stroke was defined by International Classification of Diseases, 10th Revision, diagnostic code I63 during admission. Follow-up was initiated 1 day after the third examination (S3), which was the day after the exposure assessment, and censoring occurred at death or on 31 December 2016.

Figure 1. Study population and the most common scenarios among the study population.



M– = MetS-free status; M+ = MetS-present status; MACE = major adverse cardiovascular events; MetS = metabolic syndrome; NHIS = National Health Insurance Service.
* The triangle indicates the cohort entry examination at which the baseline characteristics were recorded. Follow-up was initiated 1 day after the third examination (S3), which was the day after the exposure assessment. Those who received more than 3 health examinations are not represented.

Intergroup Analysis Adjusted for MetS Severity, Comorbidity Burden, and BMI

We performed additional comparisons between the study groups that had the same MetS presence/absence status in the period before or after the inclusion examination and added adjustment variables. The purpose was to assess the altered MACE risk for those who recovered from or developed MetS (for example, MetS-recovery vs. MetS-chronic) and investigate whether risk for MACE differed among persons with varying MetS histories (for example, MetS-recovery vs. MetS-free). In the analysis, baseline BMI, comorbidity burden as represented by the Charlson Comorbidity Index, and previous or underlying MetS severity were also adjusted for because these variables might confound the studied associations (29–32). Details of the analysis can be found in the Appendix (available at Annals.org).

Analysis of Each MetS Component

The association of a change in the status of each MetS component (presence or absence) with risk for MACE was compared with the corresponding association of a maintained component status (presence or absence). Only an alteration from the second examination (S2) or maintenance of each MetS component that persisted until the third examination (S3) was considered; transient changes were not compared. The analysis was done with the total study population without restriction to subgroups because changes in a component might

Table 1. Baseline Characteristics of the Study Population

Variable	MetS-Free	MetS-Chronic	MetS-Developed	MetS-Recovery
Participants, *n*	6 940 663	1 486 485	587 088	538 806
Clinical and demographic characteristics				
Mean age (SD), *y*	45.1 (12.9)	58.4 (12.0)	54.8 (12.6)	52.1 (12.9)
Age groups, *n* (%)				
20–39 y	2 515 016 (36.2)	110 755 (7.5)	77 462 (13.2)	97 785 (18.1)
40–59 y	3 439 355 (49.6)	635 095 (42.7)	288 373 (49.1)	282 137 (52.4)
60–79 y	944 219 (13.6)	706 274 (47.5)	211 785 (36.1)	151 203 (28.1)
≥80 y	42 073 (0.6)	34 361 (2.3)	9468 (1.6)	7681 (1.4)
Male, *n* (%)	3 757 968 (54.1)	759 556 (51.1)	329 402 (56.1)	337 648 (62.7)
Mean height (SD), *cm*	164.8 (8.8)	162.0 (9.9)	163.2 (9.8)	164.5 (9.4)
Mean weight (SD), *kg*	61.8 (10.6)	69.6 (13.1)	68.8 (12.8)	66.6 (11.5)
Mean body mass index (SD), kg/m^2	22.7 (2.7)	26.4 (3.2)	25.7 (3.1)	24.5 (2.8)
Low-income status, *n* (%)*	1 111 224 (16.0)	290 441 (19.5)	109 099 (18.6)	97 291 (18.1)
Mean Charlson Comorbidity Index score (SD)	0.6 (0.9)	1.7 (1.7)	1.2 (1.4)	0.8 (1.2)
Mean hemoglobin level (SD), *g/L*	140 (1.6)	141 (1.6)	143 (1.6)	143 (1.6)
Mean aspartate aminotransferase level (SD), *IU/L*	21.9 (21.1)	31.9 (26.3)	31.7 (27.4)	26.4 (24.8)
Mean alanine aminotransferase level (SD), *IU/L*	23.8 (16.3)	29.1 (20.3)	28.7 (20.9)	26.1 (19.9)
Mean creatinine level (SD)				
μmol/L	76.9 (16.8)	76.0 (16.8)	76.9 (16.8)	77.8 (16.8)
mg/dL	0.87 (0.19)	0.86 (0.19)	0.87 (0.19)	0.88 (0.19)
Mean estimated glomerular filtration rate (SD), $mL/min/1.73\ m^2$	92.5 (26.1)	87.2 (23.7)	88.2 (23.0)	89.8 (25.6)
Self-reported lifestyle, *n* (%)				
Moderate-to-vigorous activity				
None	2 842 832 (41.0)	719 758 (48.4)	271 442 (46.2)	230 053 (42.7)
1–2 d/wk	2 269 706 (32.7)	365 167 (24.6)	161 902 (27.6)	154 836 (28.7)
3–4 d/wk	1 159 251 (16.7)	231 683 (15.6)	91 940 (15.7)	91 375 (17)
≥5 d/wk	664 658 (9.6)	168 907 (11.4)	61 464 (10.5)	62 228 (11.5)
Unknown	4216 (0.1)	970 (0.1)	340 (0.1)	314 (0.1)
Smoking				
None	4 266 061 (61.5)	914 775 (61.5)	340 247 (58.0)	292 384 (54.3)
Former	1 033 105 (14.9)	264 423 (17.8)	108 092 (18.4)	102 604 (19.0)
Current	1 622 644 (23.4)	303 870 (20.4)	137 392 (23.4)	142 270 (26.4)
Unknown	18 853 (0.3)	3417 (0.2)	1357 (0.2)	1548 (0.3)
Alcohol intake				
None	3 348 302 (48.2)	876 175 (58.9)	316 003 (53.8)	265 820 (49.3)
Moderate	551 185 (7.9)	72 529 (4.9)	33 028 (5.6)	35 130 (6.5)
Heavy	3 034 225 (43.7)	536 629 (36.1)	237 646 (40.5)	237 445 (44.1)
Unknown	6951 (0.1)	1152 (0.1)	411 (0.1)	411 (0.1)
Mean MetS components (SD)				
Waist circumference, *cm*	77.0 (8.0)	87.9 (8.3)	86.1 (8.1)	82.3 (7.6)
Systolic blood pressure, *mm Hg*	117.7 (13.0)	130.4 (14.2)	129.1 (13.7)	123.7 (13.3)
Diastolic blood pressure, *mm Hg*	73.8 (9.1)	80.0 (9.8)	80.1 (9.6)	77.2 (9.2)
Glucose level				
mmol/L	5.10 (0.75)	6.40 (1.86)	5.92 (1.39)	5.42 (1.14)
mg/dL	91.9 (13.5)	115.4 (33.6)	106.7 (25.1)	97.6 (20.5)
Triglyceride level				
mmol/L	1.17 (0.75)	2.22 (1.62)	2.13 (1.50)	1.55 (1.04)
mg/dL	103.7 (66.5)	196.7 (143.0)	188.2 (132.8)	137.3 (92.0)
High-density lipoprotein cholesterol level,				
mmol/L	1.52 (0.37)	1.26 (0.35)	1.28 (0.36)	1.38 (0.36)
mg/dL	58.6 (14.4)	48.6 (13.6)	49.5 (13.9)	53.3 (13.8)
MetS components present at baseline (S3), *n* (%)				
0	2 788 295 (40.2)	0 (0.0)	0 (0.0)	56 756 (10.5)
1	2 570 936 (37.0)	0 (0.0)	0 (0.0)	184 304 (34.2)
2	1 581 432 (22.8)	0 (0.0)	0 (0.0)	297 746 (55.3)
3	0 (0.0)	532 446 (35.8)	344 108 (58.6)	0 (0.0)
4	0 (0.0)	606 623 (40.8)	195 135 (33.2)	0 (0.0)
5	0 (0.0)	347 416 (23.4)	47 845 (8.2)	0 (0.0)
MetS components in the prior examination (S1), *n* (%)				
0	2 992 038 (43.1)	0 (0.0)	27 736 (4.7)	0 (0.0)
1	2 575 036 (37.1)	0 (0.0)	157 855 (26.9)	0 (0.0)
2	1 373 589 (19.8)	0 (0.0)	401 497 (68.4)	0 (0.0)
3	0 (0.0)	653 029 (43.9)	0 (0.0)	439 305 (81.5)
4	0 (0.0)	577 276 (38.8)	0 (0.0)	90 660 (16.8)
5	0 (0.0)	256 180 (17.2)	0 (0.0)	8841 (1.6)

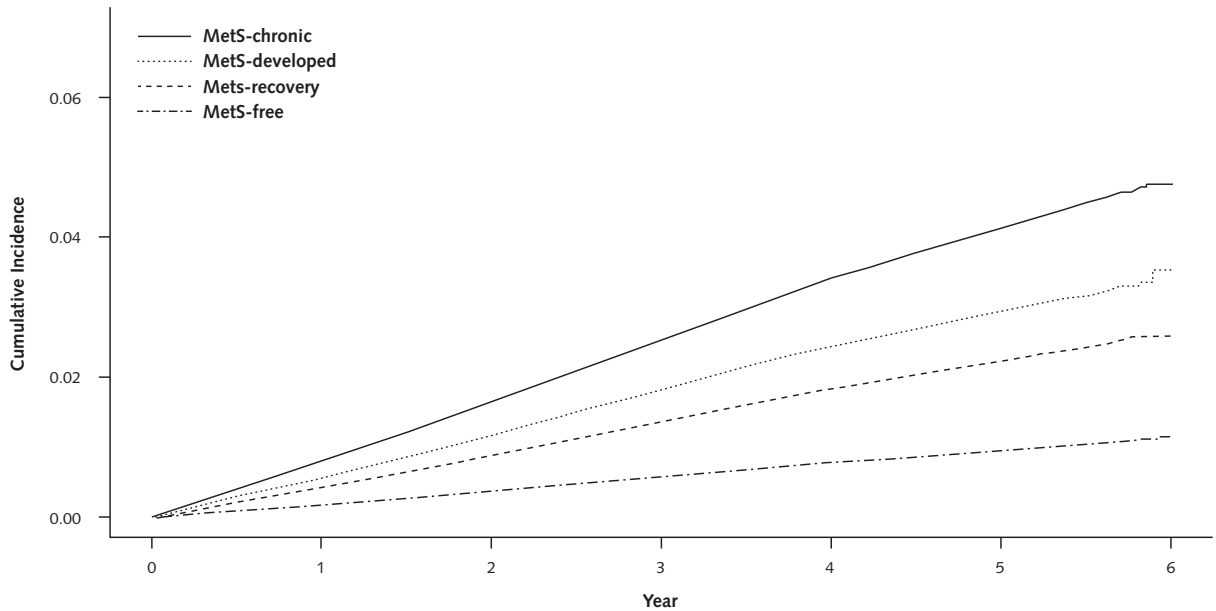
MetS = metabolic syndrome.
* Those who were included in the lowest quartile of the required insurance fee or who received free medical care.

occur in any of the subgroups. Status of the other MetS components that were not the main explanatory variable were included in the regression models as categorical variables and were categorized as chronically persistent, consistently free, developed or recovered from a certain time point, or inconsistent among the first 3 health screenings (S1, S2, and S3).

Statistical Analysis

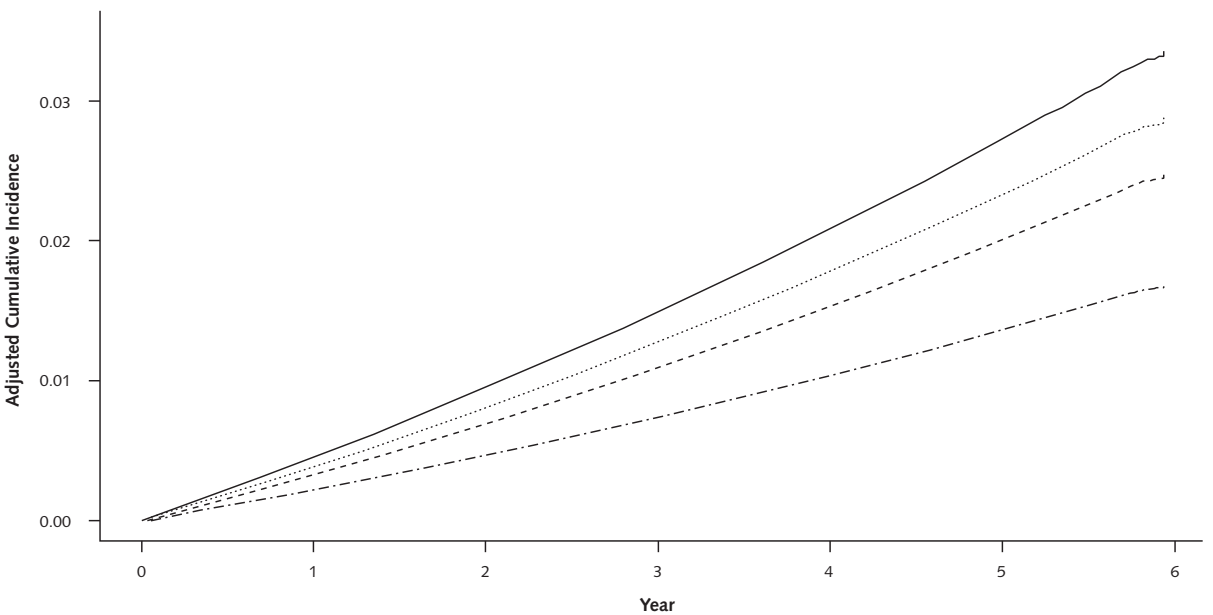
Continuous variables are presented as means (SDs), and categorical variables are presented as numbers (percentages). Poisson regression was done to calculate the incidence rate ratios (IRRs) and 95% CIs, and the following variables were adjusted in the base multivariable model: age; sex; low-income status; base-

Figure 2. Unadjusted and adjusted curves showing the cumulative incidence probability of MACE among the study groups.



At risk, *n*

MetS-chronic	1 486 485	1 472 453	1 454 696	889 224	425 348	264 575	7
MetS-developed	587 088	583 048	577 767	360 578	180 520	114 048	5
MetS-recovery	538 806	535 851	531 772	364 612	214 830	144 193	2
MetS-free	6 940 663	6 923 811	6 899 153	4 800 789	3 023 745	2 052 284	17



Adjusted Cumulative Incidence per 1000 Persons (95% CI)

MetS-chronic	4.56 (4.49–4.62)	9.56 (9.45–9.66)	15.01 (14.86–15.16)	20.99 (20.78–21.19)	27.37 (27.09–27.65)	33.50 (32.75–34.25)
MetS-developed	3 88 (3.80–3.96)	8.15 (8.00–8.29)	12.81 (12.58–13.03)	17.93 (17.62–18.24)	23.41 (23.00–23.82)	28.69 (27.93–29.46)
MetS-recovery	3.32 (3.25–3.40)	6.99 (6.84–7.13)	11.00 (10.77–11.22)	15.41 (15.10–15.72)	20.14 (19.73–20.55)	24.71 (24.00–25.42)
MetS-free	2.24 (2.21–2.27)	4.72 (4.67–4.77)	7.44 (7.37–7.51)	10.45 (10.35–10.55)	13.69 (13.55–13.82)	16.83 (16.45–17.21)

The curve and table show the Kaplan–Meier survival curve and number of persons at risk for MACE (*top*). The curve and table show the adjusted survival curve for MACE with adjusted cumulative incidences (per 1000 persons) at each time point (*bottom*). The curve was adjusted for age; sex; low-income status; baseline estimated glomerular filtration rate; and hemoglobin, aspartate aminotransferase, and alanine aminotransferase levels. The *x*-axes indicate the time from follow-up initiation (years), and the *y*-axes indicate the unadjusted or adjusted cumulative incidence probability. MACE = major adverse cardiovascular events; MetS = metabolic syndrome.

Table 2. Risk for MACE and Individual Outcomes According to the Dynamic MetS Status

Outcomes	Events, *n*	Person-Years	Incidence Rate per 1000 Person-Years	Unadjusted Model		Multivariable Model*	
				IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
MACE (composite)							
MetS-free	50 564	26 383 975	1.92	1 (reference)		1 (reference)	
MetS-recovery	9141	2 010 212	4.55	2.37 (2.32–2.43)	<0.001	1.48 (1.44–1.51)	<0.001
MetS-developed	12 463	2 059 755	6.05	3.16 (3.10–3.22)	<0.001	1.71 (1.67–1.74)	<0.001
MetS-chronic	43 867	5 150 169	8.52	4.44 (4.39–4.50)	<0.001	2.01 (1.98–2.04)	<0.001
Acute myocardial infarction							
MetS-free	16 333	26 383 975	0.62	1 (reference)		1 (reference)	
MetS-recovery	2732	2 010 212	1.36	2.20 (2.11–2.29)	<0.001	1.47 (1.41–1.53)	<0.001
MetS-developed	3640	2 059 755	1.77	2.86 (2.75–2.96)	<0.001	1.70 (1.64–1.76)	<0.001
MetS-chronic	11 760	5 150 169	2.28	3.69 (3.60–3.78)	<0.001	1.89 (1.84–1.93)	<0.001
Revascularization							
MetS-free	8167	26 383 975	0.31	1 (reference)		1 (reference)	
MetS-recovery	1732	2 010 212	0.86	2.78 (2.64–2.93)	<0.001	1.76 (1.67–1.85)	<0.001
MetS-developed	2686	2 059 755	1.30	4.21 (4.03–4.40)	<0.001	2.40 (2.30–2.51)	<0.001
MetS-chronic	10 666	5 150 169	2.07	6.69 (6.50–6.89)	<0.001	3.30 (3.20–3.40)	<0.001
Acute ischemic stroke							
MetS-free	26 064	26 383 975	0.99	1 (reference)		1 (reference)	
MetS-recovery	4677	2 010 212	2.33	2.36 (2.28–2.43)	<0.001	1.40 (1.36–1.44)	<0.001
MetS-developed	6137	2 059 755	2.98	3.02 (2.93–3.10)	<0.001	1.52 (1.48–1.56)	<0.001
MetS-chronic	21 441	5 150 169	4.16	4.21 (4.14–4.29)	<0.001	1.72 (1.69–1.76)	<0.001

IRR = incidence rate ratio; MACE = major adverse cardiovascular events (composite of acute myocardial infarction, revascularization, and acute ischemic stroke); MetS = metabolic syndrome.
* Adjusted for age; sex; low-income status (the lowest quartile in the nation); baseline estimated glomerular filtration rate; and hemoglobin, aspartate aminotransferase, and alanine aminotransferase levels.

line estimated glomerular filtration rate; and hemoglobin, alanine aminotransferase, and aspartate aminotransferase levels. Kaplan–Meier survival curves were plotted using the PROC LIFETEST command in SAS, version 9.4 (SAS Institute). Adjusted survival curve for the Cox proportional hazards model was plotted using the PROC PHREG command in SAS, with adjustment for the same variables included in the above base model. Several variables, including the Charlson Comorbidity Index, BMI, and severity of MetS, were added to the base model, and adjusted IRRs were calculated for the intergroup analysis results (Appendix). There were no missing variables in the regression analyses because we excluded persons with missing information at baseline or at parameters to define MetS status. Only the lifestyle variables, which were obtained from self-reported questionnaires and not imputed, included missing information but not included in the regression analyses. All statistical analyses were done using SAS, and 2-sided *P* values less than 0.05 were considered statistically significant.

Role of the Funding Source

This work was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI17C0530). The funder played no role in the performance of the study, and the study was done independently by the authors.

RESULTS

Study Population

Among 27 161 051 persons who received health screenings during the study period, we identified 12 993 170 who had 3 or more health examinations (Figure 1). After excluding an additional 77 450 persons who had information missing from their first 3 screening results or in baseline laboratory findings, 12 915 720 had 3 or more health examinations with an identifiable MetS status. We additionally applied the eligibility criteria, and those with an inconsistent MetS status, history of MACE, or underlying kidney function impairment were excluded, yielding 9 553 042 persons in the final study population. Median follow-up was 3.54 years (interquartile range, 2.63 to 5.05 years). Among these persons, 6 940 663 (72.7%) were included in the MetS-free group, 1 486 485 (15.6%) were included in the MetS-chronic group, 587 088 (6.1%) were included in the MetS-developed group, and 538 806 (5.6%) were included in the MetS-recovery group.

Baseline Characteristics

Baseline characteristics according to dynamic MetS status are shown in Table 1. The MetS-chronic group consisted of the oldest population among the studied subgroups. The MetS-free and MetS-recovery groups had the lowest proportions of the population who did not exercise among all of the groups analyzed. Heavy or moderate alcohol consumption was more common in the subgroups with younger average ages. The MetS-developed and MetS-recovery groups had relatively similar characteristics; nevertheless, the MetS-developed group included a higher percentage of older persons and persons with high BMIs or Charlson Comorbidity Index scores than the MetS-recovery

group. In addition, persons in the MetS-chronic group had 5 MetS components at baseline (S3) or in the prior examination (S1) more often than persons in the other groups. Having 2 components in prior examinations (S1) was most common in the MetS-developed group, and having 3 components at the first examination (S1) was most common in the MetS-recovery group. Approximately 40% of persons in the MetS-free group did not meet any MetS criterion in either the prior examination (S1) or the entry examination (S3).

MACE Risk According to the Dynamic MetS Status

The incidence rate of MACE was highest in the MetS-chronic group (43 867 events during 5 150 169 person-years of follow-up, incidence rate of 8.52 per 1000 person-years) throughout follow-up, followed by the MetS-developed group (12 463 events during 2 059 755 person-years of follow-up, incidence rate of 6.05 per 1000 person-years), MetS-recovery group (9141 events during 2 010 212 person-years of follow-up, incidence rate of 4.55 per 1000 person-years), and MetS-free group (50 564 events during 26 383 975 person-years of follow-up, incidence rate of 1.92 per 1000 person-years) (Figure 2). Risk for individual outcomes consisting of MACE showed a distribution similar to that for total MACE, even in the multivariable analysis (Table 2).

Intergroup Comparison

In further intergroup comparison (Table 3), MetS recovery was associated with an approximately 80% MACE adjusted IRR compared with the MetS-chronic group even after controlling for the previous severity of MetS, BMI, and comorbidity burden. When we compared the MetS-developed group with the MetS-free group, the development of MetS was associated with a higher risk for MACE.

In addition, we compared the MACE risk between the MetS-recovery group and the MetS-free group, because persons in those groups had the same MetS-free status at follow-up but different MetS histories. We still found a higher risk for MACE in the MetS-recovery group than in the MetS-free group when controlling for the severity of MetS at baseline. A similar comparison was done between the MetS-developed and MetS-chronic groups. Both groups had similar MACE risk without significant differences after adjustment for baseline severity of MetS.

Components of MetS and MACE

The development of or recovery from each MetS component was significantly associated with the risk for MACE and individual outcomes in the total study population (Appendix Tables 1 and 2, available at Annals.org). When differences in the strengths of the associations were compared with adjustment for other MetS component status changes and other clinical variables (Figure 3), development of elevated blood pressure criterion was associated with the largest adjusted MACE IRR among all of the components analyzed. Although increased waist circumference and impaired glucose tolerance were associated with relatively small increases in risk, the changes were significant. Regarding recovery from a component, elevated blood pressure was again the criterion associated with the largest reduction in MACE risk in both the univariable and multivariable analyses, followed by the impaired glucose tolerance criterion.

Table 3. MACE Risk Comparison Between Study Groups With the Same MetS Status in the Previous Period or After the Inclusion Period

Compared Subgroups	Model 1: Base Model*		Model 2: Adjusted for Body Mass Index and Charlson Comorbidity Index†		Model 3: Adjusted for Number of MetS Components‡		Model 4: Adjusted for MetS Laboratory Results§	
	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Significance of recovery from or development of MetS (comparison between groups with the same MetS presence/absence status at S1)								
MetS-recovery vs. MetS-chronic	0.71 (0.69–0.73)	<0.001	0.82 (0.80–0.84)	<0.001	0.83 (0.81–0.86)	<0.001	0.85 (0.83–0.87)	<0.001
MetS-developed vs. MetS-free	1.71 (1.67–1.74)	<0.001	1.49 (1.46–1.52)	<0.001	1.40 (1.4–1.43)	<0.001	1.36 (1.33–1.39)	<0.001
Significance of previous history of MetS (comparison between groups with the same MetS presence/absence status at S2 and S3)								
MetS-recovery vs. MetS-free	1.48 (1.44–1.51)	<0.001	1.40 (1.37–1.43)	<0.001	1.06 (1.03–1.09)	<0.001	1.19 (1.16–1.22)	<0.001
MetS-developed vs. MetS-chronic	0.83 (0.82–0.85)	<0.001	0.90 (0.89–0.92)	<0.001	1.01 (0.98–1.04)	0.45	1.00 (0.98–1.02)	0.70

IRR = incidence rate ratio; MACE = major adverse cardiovascular events (composite of acute myocardial infarction, revascularization, and acute ischemic stroke); MetS = metabolic syndrome.

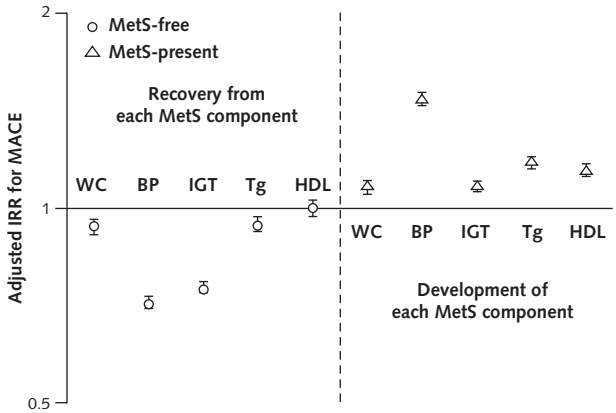
* Adjusted for age; sex; low-income status (the lowest quartile of required medical fee); baseline estimated glomerular filtration rate; and hemoglobin, aspartate aminotransferase, and alanine aminotransferase levels.

† Body mass index and Charlson Comorbidity Index were added to model 1.

‡ The number of harmonizing MetS criteria present was added to model 2. As a comparison of those who had the same MetS status in the previous examination (e.g., MetS-recovery vs. MetS-chronic or MetS-developed vs. MetS-free groups), the number of MetS components in the previous examination (S1) was adjusted. When those who had the same MetS status in S2 and S3 (e.g., MetS-recovery vs. MetS-free or MetS-developed vs. MetS-chronic groups) were compared, the number at the baseline examination (S3) was adjusted.

§ A similar adjustment was done, but the exact values of waist circumference; systolic blood pressure; diastolic blood pressure; and fasting glucose, triglyceride, and high-density lipoprotein cholesterol levels were included in the multivariable model instead of the number of MetS components.

Figure 3. Components of the MetS criteria and their association with the risk for MACE.



The associations of the risk for development or recovery of each component were investigated separately. The *y*-axis indicates the adjusted IRRs in $\log_2$ scale, and the vertical lines signify the CIs. The multivariable model was adjusted for age; sex; low-income status (the lowest quartile in the nation); baseline estimated glomerular filtration rate; and hemoglobin, aspartate aminotransferase, and alanine aminotransferase levels. In addition, to account for the statuses of other MetS components that were not the main explanatory variable, these statuses were included in the regression models as categorical variables and were scored as chronically persistent, consistently free, developed or recovered from certain a time point, or inconsistent among the studied health examinations. The presence of each component of MetS was determined by the harmonizing criteria. BP = blood pressure; HDL = high-density lipoprotein; IGT = impaired glucose tolerance; IRR = incidence rate ratio; MACE = major adverse cardiovascular events; MetS = metabolic syndrome; Tg = triglyceride; WC = waist circumference.

DISCUSSION

We found that MACE risk changed significantly according to the dynamic MetS status in a nationwide population-based cohort. Compared with persons with chronic MetS, those who recovered from MetS had a reduced risk for MACE. In addition, persons who developed MetS had a significantly higher risk for MACE than those who remained MetS-free.

The main strength of this study is that we obtained our main findings from nationwide data that included a large number of health screenings and complete outcomes. The presence of MetS at a single time point is a known predictor of cardiovascular outcomes (2, 3, 14, 29, 33), but whether changes in MetS status are associated with alterations of MACE risk has yet to be reported on a population scale. Herein, we analyzed a population-based database, including information from periodic health checkups, and successfully defined dynamic MetS status with the exclusion of transient changes. The prevalence of MetS during follow-up was considered acceptable, considering that we excluded persons with renal function impairment or a history of MACE (34). Although the findings can be explained by traditional concepts of controlling metabolic risk factors to reduce MACE risk, such nationwide results provide unique evidence supporting the benefits of MetS recovery and prevention (21).

Recovery from MetS was associated with a significantly lower MACE risk than that of persons in the MetS-chronic group. On the other hand, those who developed MetS showed a significantly higher risk for MACE than the MetS-free group. The associations remained significant even after adjustment for BMI, Charlson Comorbidity Index, and past MetS severity. Thus, the benefit of MetS recovery, or harm associated with MetS development, may present regardless of the underlying MetS severity, obesity, or comorbidity burden. Health care providers may consider these results when planning a public health strategy to alleviate the burden of MACE.

Among MetS criteria, development of the elevated blood pressure criterion was related to the largest increase in MACE risk. Conversely, recovery from previously elevated blood pressure was associated with the largest reduction in risk. This result may emphasize the potential clinical importance of the elevated blood pressure criterion among the MetS components. That changes in waist circumference were associated with a relatively small adjusted MACE IRR in the multivariable models possibly indicates that the criterion may be a predisposing factor for other MetS components (35, 36). However, which MetS component should be primarily prevented to decrease the risk for MACE should be determined in a future prospective study with detailed information on temporal precedence.

Notably, MACE risk was higher in the MetS-recovery group than in the MetS-free group, although both groups were equally free from MetS during follow-up. Given that we made efforts to adjust for the metabolic or obesity burden at the time of inclusion, this finding may indicate the clinical significance of a MetS history. Reversal of MetS damage to the cardiovascular system may require a longer period of recovery (37). Our study encourages health care providers to pay attention to a history of MetS even in persons who are currently free from MetS. Further studies focusing on the clinical importance of a MetS history may provide important evidence that can be used to guide clinical practice. The group that developed MetS had risk for MACE similar to that of the group with chronic MetS after adjustment for underlying severity. This suggests that when severity is similar, persons with new-onset MetS may have risk for MACE comparable to those with chronic MetS.

Finally, we showed that the repetitive assessment of MetS with easily collected variables in a general health screening could be a simple tool for evaluating MACE risk in a population. Although the innate limitation of a cluster of traditional cardiovascular risk factors is present (38), our study supports the clinical value of the MetS concept because it combines changes in various metabolic risks in a practical manner.

Our study has limitations. First, its retrospective design may include hidden social or clinical confounding factors. A future prospective study is necessary to confirm whether such public interventions could prevent consequential MACE (18, 20). This future study should also aim to resolve potential inaccuracy among the ap-

plied diagnostic codes. Second, our study's follow-up is relatively short. On the other hand, the limitation may be interpreted as that only a few years of follow-up are necessary to observe the significant associations between the MACE risk and the dynamic MetS status. However, longer follow-up would allow evaluation of the long-term effects of the MetS status and mortality outcomes. Third, a detailed analysis of the association between self-reported lifestyle variables and the risk for MACE should be considered. However, because the characteristics of the cohorts themselves were strongly correlated to the investigated lifestyles–women were more commonly nonsmokers and younger persons were more likely to consume alcohol–additional studies should be done with a clear dissection of our study population. Fourth, the definition of our study population made it impossible to examine whether a short-term change or fluctuation in MetS status is associated with a different MACE risk. Finally, our study cohort, although it was one of the largest cohorts in which MetS was evaluated, included persons only from a single country and the prevalence of MetS might not be the same in other nations.

In conclusion, the dynamic MetS status of a population is closely associated with different risks for MACE. Further trials with population-scale interventions to reduce the burden of MACE by preventing or reducing MetS are warranted to confirm the benefits of recovery from or prevention of MetS.

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Note: This study used the National Health Insurance Database managed by the National Health Insurance Service of Korea. The approach was approved by the organization (NHIS-2018-1-136).

Grant Support: This work was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI17C0530).

Disclosures: Dr. Kim reports a grant from the Ministry of Health and Welfare, Republic of Korea. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-0563.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available from Dr. Kim (e-mail, dkkim73@gmail.com). *Data set:* Data are available through the Korean National Health Insurance Sharing Service. Researchers who wish to access the data can apply at (https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do) and request access to NHIS-2018-1-136.

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Appendix

Details About the Intergroup Analysis and Multivariable Models

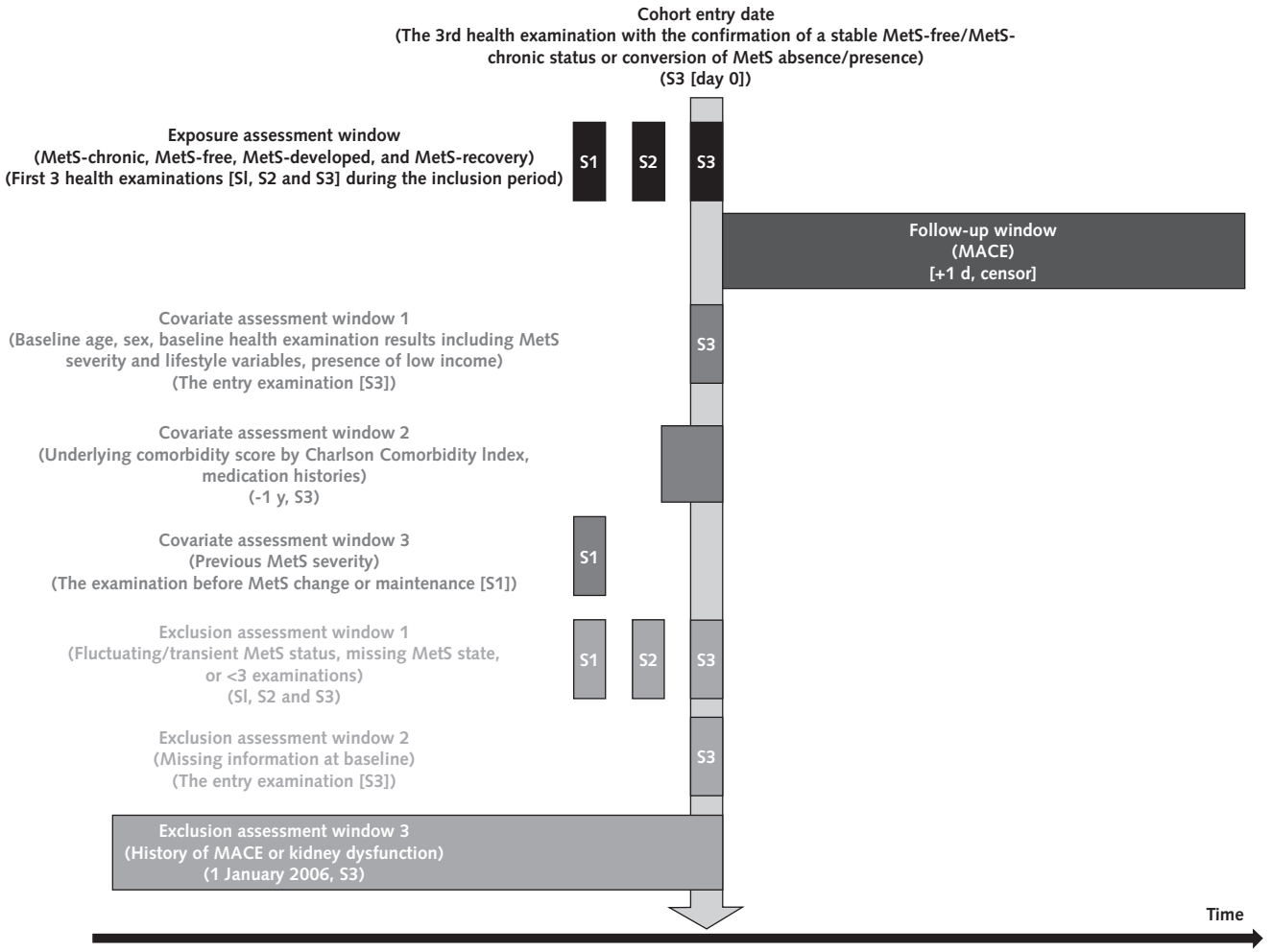
The main aim of the intergroup analysis was to assess the association between the development of or recovery from metabolic syndrome (MetS) and the risk for major adverse cardiovascular events (MACE) compared with persons who had a consistent MetS status.

Differing body mass index (BMI), comorbidity, or MetS severity are potentially understood as distinct characteristics of different MetS subgroups. For example, persons with chronic MetS may have had naturally higher BMIs, more comorbidities, or more severe MetS than those in the MetS-recovery group, hindering them from recovering from preexisting MetS. Therefore, in the base multivariable model, those variables were not used for adjustment, and the model included the following other potential confounders: age; sex; low-income status (the lowest quartile of the required medical fee); baseline estimated glomerular filtration rate; and hemoglobin, aspartate aminotransferase, and alanine aminotransferase levels.

Because the BMI, comorbidity burden, or underlying MetS severity may also confound the association between an altered MetS status and the risk for MACE, we constructed additional multivariable models. In the first additional multivariable model, the baseline BMI and Charlson Comorbidity Index were added to the variables included in the base model to assess whether the development of or recovery from MetS was associated with an altered MetS risk in persons with similar BMIs or comorbidity burdens.

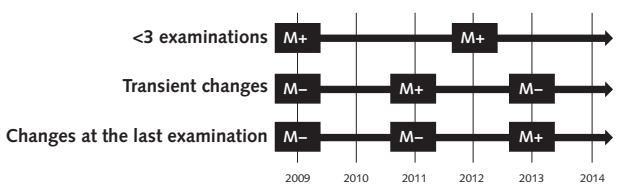
Next, the underlying or previous severity of MetS was added to the variables included in the above multivariable model. The severity of MetS was determined by the following 2 definitions: the number of MetS components present, and the actual measured values of the components in the harmonizing MetS criteria. The 2 definitions were complementary because the number of preexisting MetS components could not reflect the continuous information (for example, high glucose values) in each MetS component, and the actual values of the MetS components could be affected by medications taken. We included the severity of MetS before the difference in the MetS presence or absence status appeared between the 2 subgroups. For example, the MetS severity from the examination before a change in the MetS state occurred (S1) was adjusted for to control for the previous MetS severity in the analysis of the risk difference between the MetS-recovery and MetS-chronic groups. The baseline severity of MetS at the follow-up initiation (S3) was adjusted for between persons with the same MetS status during the follow-up (for example, MetS-recovery group vs. MetS-free group).

Appendix Figure 1. Graphical description of time windows to determine the study population, follow-up, covariate assessment, and exclusion.



MACE = major adverse cardiovascular events; MetS = metabolic syndrome.

Appendix Figure 2. Examples of possible scenarios of exclusion.



The figure shows several possible scenarios for exclusion: persons with fewer than 3 health examinations even if they had persistent MetS statuses during the study period, as the persistency or alteration was not certain; persons with transient changes because persistent alteration or maintenance of their MetS status was unidentifiable; and persons with altered MetS statuses at the last examination, as designating the baseline at the time of change was identified (2013 in the example shown in the figure) would not assure the persistency of the change. M– = MetS-free status; M+ = MetS-present status; MetS = metabolic syndrome.

Appendix Table 1. Risk for MACE According to the Developed MetS Component as Determined by Analyses of Persons Who Had Persistent Development or Free State of the Analyzed Component in the Total Study Population

Component	Outcome	Component Status	Patients Included, *n*	Incidence Rate per 1000 Person-Years	Univariable Model		Multivariable Model*	
					IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Increased waist circumference	MACE	Persistently absent	6 289 424	2.37	1 (reference)		1 (reference)	
		Developed and maintained	756 626	3.98	1.68 (1.65–1.72)	<0.001	1.08 (1.05–1.10)	<0.001
	Acute myocardial infarction	Persistently absent	6 289 424	0.74	1 (reference)		1 (reference)	
		Developed and maintained	756 626	1.13	1.53 (1.48–1.59)	<0.001	1.05 (1.01–1.10)	0.015
	Revascularization	Persistently absent	6 289 424	0.75	1 (reference)		1 (reference)	
		Developed and maintained	756 626	1.29	1.72 (1.66–1.78)	<0.001	1.09 (1.05–1.14)	<0.001
	Acute ischemic stroke	Persistently absent	6 289 424	1.20	1 (reference)		1 (reference)	
		Developed and maintained	756 626	2.05	1.71 (1.66–1.76)	<0.001	1.08 (1.05–1.11)	<0.001
Elevated blood pressure	MACE	Persistently absent	3 933 103	1.13	1 (reference)		1 (reference)	
		Developed and maintained	1 206 497	3.14	2.78 (2.72–2.84)	<0.001	1.47 (1.44–1.51)	<0.001
	Acute myocardial infarction	Persistently absent	3 933 103	0.43	1 (reference)		1 (reference)	
		Developed and maintained	1 206 497	1.00	2.32 (2.23–2.41)	<0.001	1.34 (1.29–1.39)	<0.001
	Revascularization	Persistently absent	3 933 103	0.31	1 (reference)		1 (reference)	
		Developed and maintained	1 206 497	0.97	3.18 (3.05–3.32)	<0.001	1.46 (1.40–1.52)	<0.001
	Acute ischemic stroke	Persistently absent	3 933 103	0.53	1 (reference)		1 (reference)	
		Developed and maintained	1 206 497	1.59	3.00 (2.91–3.10)	<0.001	1.58 (1.53–1.64)	<0.001
Impaired glucose tolerance	MACE	Persistently absent	5 087 204	2.02	1 (reference)		1 (reference)	
		Developed and maintained	1 229 736	3.85	1.91 (1.88–1.94)	<0.001	1.08 (1.06–1.10)	<0.001
	Acute myocardial infarction	Persistently absent	5 087 204	0.65	1 (reference)		1 (reference)	
		Developed and maintained	1 229 736	1.19	1.83 (1.78–1.89)	<0.001	1.10 (1.06–1.13)	<0.001
	Revascularization	Persistently absent	5 087 204	0.56	1 (reference)		1 (reference)	
		Developed and maintained	1 229 736	1.19	2.11 (2.04–2.18)	<0.001	1.06 (1.03–1.10)	<0.001
	Acute ischemic stroke	Persistently absent	5 087 204	1.05	1 (reference)		1 (reference)	
		Developed and maintained	1 229 736	1.96	1.87 (1.83–1.92)	<0.001	1.07 (1.04–1.10)	<0.001
Elevated triglyceride level	MACE	Persistently absent	5 277 493	2.03	1 (reference)		1 (reference)	
		Developed and maintained	1 049 884	4.01	1.97 (1.94–2.01)	<0.001	1.18 (1.15–1.20)	<0.001
	Acute myocardial infarction	Persistently absent	5 277 493	0.62	1 (reference)		1 (reference)	
		Developed and maintained	1 049 884	1.18	1.92 (1.85–1.98)	<0.001	1.22 (1.18–1.27)	<0.001
	Revascularization	Persistently absent	5 277 493	0.50	1 (reference)		1 (reference)	
		Developed and maintained	1 049 884	1.28	2.56 (2.48–2.65)	<0.001	1.37 (1.32–1.43)	<0.001
	Acute ischemic stroke	Persistently absent	5 277 493	1.12	1 (reference)		1 (reference)	
		Developed and maintained	1 049 884	2.05	1.83 (1.78–1.87)	<0.001	1.11 (1.07–1.14)	<0.001
Decreased high-density lipoprotein cholesterol level	MACE	Persistently absent	5 977 136	2.21	1 (reference)		1 (reference)	
		Developed and maintained	1 025 187	5.00	2.27 (2.23–2.31)	<0.001	1.14 (1.12–1.17)	<0.001
	Acute myocardial infarction	Persistently absent	5 977 136	0.69	1 (reference)		1 (reference)	
		Developed and maintained	1 025 187	1.47	2.14 (2.08–2.21)	<0.001	1.16 (1.12–1.20)	<0.001
	Revascularization	Persistently absent	5 977 136	0.63	1 (reference)		1 (reference)	
		Developed and maintained	1 025 187	1.68	2.67 (2.59–2.76)	<0.001	1.37 (1.32–1.42)	<0.001
	Acute ischemic stroke	Persistently absent	5 977 136	1.17	1 (reference)		1 (reference)	
		Developed and maintained	1 025 187	2.49	2.13 (2.08–2.18)	<0.001	1.04 (1.01–1.07)	0.02

IRR = incidence rate ratio; MACE = major adverse cardiovascular events (composite of acute myocardial infarction, revascularization, and acute ischemic stroke); MetS = metabolic syndrome.
* Adjusted for age, sex, low-income status, baseline estimated glomerular filtration rate, hemoglobin level, aspartate aminotransferase level, alanine aminotransferase level, hemoglobin level, and status (chronic, absent, developed, recovered, or inconsistent) of other MetS components during the study period.

Appendix Table 2. Risk for MACE According to the Recovered MetS Component as Determined by Analyses of Persons Who Consistently Recovered From or Exhibited Chronically Present State of the Analyzed Component in the Total Study Population

Component	Outcome	Component Status	Patients Included, *n*	Incidence Rate per 1000 Person-Years	Univariable Model		Multivariable Model*	
					IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Increased waist circumference	MACE	Recovered and maintained	653 945	4.51	0.70 (0.68–0.71)	<0.001	0.94 (0.91–0.96)	<0.001
		Persistently present	1 301 579	6.48	1 (reference)		1 (reference)	
	Acute myocardial infarction	Recovered and maintained	653 945	1.27	0.69 (0.67–0.72)	<0.001	0.90 (0.86–0.94)	<0.001
		Persistently present	1 301 579	1.83	1 (reference)		1 (reference)	
	Revascularization	Recovered and maintained	653 945	1.41	0.69 (0.67–0.72)	<0.001	0.93 (0.89–0.97)	<0.001
		Persistently present	1 301 579	2.04	1 (reference)		1 (reference)	
	Acute ischemic stroke	Recovered and maintained	653 945	2.37	0.70 (0.68–0.73)	<0.001	0.95 (0.92–0.99)	0.004
		Persistently present	1 301 579	3.37	1 (reference)		1 (reference)	
Elevated blood pressure	MACE	Recovered and maintained	1 081 826	2.58	0.34 (0.33–0.35)	<0.001	0.71 (0.70–0.73)	<0.001
		Persistently present	2 370 501	7.61	1 (reference)		1 (reference)	
	Acute myocardial infarction	Recovered and maintained	1 081 826	0.86	0.43 (0.42–0.45)	<0.001	0.81 (0.78–0.84)	<0.001
		Persistently present	2 370 501	1.99	1 (reference)		1 (reference)	
	Revascularization	Recovered and maintained	1 081 826	0.81	0.32 (0.31–0.33)	<0.001	0.66 (0.63–0.69)	<0.001
		Persistently present	2 370 501	2.52	1 (reference)		1 (reference)	
	Acute ischemic stroke	Recovered and maintained	1 081 826	1.29	0.32 (0.31–0.33)	<0.001	0.69 (0.67–0.71)	<0.001
		Persistently present	2 370 501	4.04	1 (reference)		1 (reference)	
Impaired glucose tolerance	MACE	Recovered and maintained	1 043 041	3.20	0.40 (0.39–0.41)	<0.001	0.75 (0.74–0.77)	<0.001
		Persistently present	1 258 143	8.04	1 (reference)		1 (reference)	
	Acute myocardial infarction	Recovered and maintained	1 043 041	0.97	0.46 (0.45–0.48)	<0.001	0.80 (0.77–0.84)	<0.001
		Persistently present	1 258 143	2.09	1 (reference)		1 (reference)	
	Revascularization	Recovered and maintained	1 043 041	1.01	0.35 (0.33–0.36)	<0.001	0.68 (0.65–0.70)	<0.001
		Persistently present	1 258 143	2.91	1 (reference)		1 (reference)	
	Acute ischemic stroke	Recovered and maintained	1 043 041	1.64	0.40 (0.39–0.41)	<0.001	0.76 (0.74–0.79)	<0.001
		Persistently present	1 258 143	4.09	1 (reference)		1 (reference)	
Elevated triglyceride level	MACE	Recovered and maintained	892 031	3.95	0.62 (0.60–0.63)	<0.001	0.94 (0.92–0.97)	<0.001
		Persistently present	1 610 078	6.42	1 (reference)		1 (reference)	
	Acute myocardial infarction	Recovered and maintained	892 031	1.16	0.63 (0.60–0.65)	<0.001	0.88 (0.84–0.92)	<0.001
		Persistently present	1 610 078	1.86	1 (reference)		1 (reference)	
	Revascularization	Recovered and maintained	892 031	1.28	0.52 (0.50–0.54)	<0.001	0.88 (0.85–0.92)	<0.001
		Persistently present	1 610 078	2.46	1 (reference)		1 (reference)	
	Acute ischemic stroke	Recovered and maintained	892 031	2.03	0.67 (0.65–0.69)	<0.001	0.98 (0.95–1.01)	0.19
		Persistently present	1 610 078	3.04	1 (reference)		1 (reference)	
Decreased high-density lipoprotein cholesterol level	MACE	Recovered and maintained	827 406	3.86	0.55 (0.53–0.56)	<0.001	1.00 (0.97–1.03)	0.98
		Persistently present	1 087 848	7.06	1 (reference)		1 (reference)	
	Acute myocardial infarction	Recovered and maintained	827 406	1.15	0.60 (0.58–0.63)	<0.001	1.00 (0.95–1.05)	0.97
		Persistently present	1 087 848	1.91	1 (reference)		1 (reference)	
	Revascularization	Recovered and maintained	827 406	1.23	0.49 (0.47–0.51)	<0.001	0.87 (0.83–0.91)	<0.001
		Persistently present	1 087 848	2.51	1 (reference)		1 (reference)	
	Acute ischemic stroke	Recovered and maintained	827 406	1.99	0.57 (0.56–0.59)	<0.001	1.09 (1.05–1.13)	<0.001
		Persistently present	1 087 848	3.47	1 (reference)		1 (reference)	

IRR = incidence rate ratio; MACE = major adverse cardiovascular events (composite of acute myocardial infarction, revascularization, and acute ischemic stroke); MetS = metabolic syndrome.
* Adjusted for age, sex, low-income status, baseline estimated glomerular filtration rate, hemoglobin level, aspartate aminotransferase level, alanine aminotransferase level, hemoglobin level, and status (chronic, absent, developed, recovered, or inconsistent) of other MetS components during the study period.