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Metabolic syndrome and risk of monoclonal gammopathy of undetermined significance: a large Korean cohort study

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Disclosures

No conflicts of interest to disclose.

Author Contributions

JYL and KH designed the experiments, interpreted the data, and wrote the manuscript; JYL, KH, and SMB performed the experiments, analyzed the data, prepared the figures, and drafted the manuscript; EJJ, SK, SAK, JOL, and SMB contributed to the analysis and interpretation of the results; and all authors critically reviewed the manuscript.

Data-sharing statement

All data generated or analyzed during this study are included in this published article and its supplementary information files. Additional data is available from the corresponding author upon reasonable and justified requests.

Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder with a risk of progression to multiple myeloma. Metabolic syndrome (MetS) is implicated in cancer development, yet its association with MGUS remains unclear. We examined MetS as a risk factor for MGUS in a large Korean cohort. In a retrospective cohort study using the National Health Information Database, we analyzed 4,453,504 adults undergoing health checkups in 2012, followed through 2022. MetS was defined by NCEP-ATP III criteria. Over a median 9.3-year follow-up, 1,241 MGUS cases were identified. MetS was associated with a 28% increased MGUS risk (HR: 1.28, 95% CI: 1.14-1.44). Risk escalated with more MetS components, peaking at 76% for five components (HR: 1.76, 95% CI: 1.35-2.30). Low HDL cholesterol, hypertension, and central obesity were key risk factors, with higher risks in males and younger adults (20–39 years). Longitudinal analysis showed MetS onset (HR: 1.25, 95% CI: 1.06-1.47) or persistence (HR: 1.25, 95% CI: 1.06-1.48) increased MGUS risk compared to persistent MetS absence, whereas MetS resolution showed no significant risk increase over persistent MetS absence. MetS increases MGUS risk, particularly in males and younger individuals. Resolving MetS may mitigate MGUS risk, supporting targeted metabolic interventions.

Keywords: Monoclonal Gammopathy of Undetermined Significance, Metabolic Syndrome Risk, Prevention

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder characterized by the presence of monoclonal protein in the serum or urine without evidence of end-organ damage or malignancy, such as multiple myeloma or amyloidosis.[1] MGUS is the most common form of monoclonal gammopathy, with a prevalence of approximately 3-4% in individuals aged ≥ 50 years in Western populations and slightly lower rates in Asian populations, including South Korea.[2-4] It carries a 1% annual progression risk to multiple myeloma (MM) or related lymphoproliferative disorders.[5] Studies have identified potentially modifiable risk factors for MGUS, such as obesity-related comorbidities and lifestyle factors, linking obesity and consumption of artificially sweetened beverages to an increased risk of MGUS through chronic inflammation and metabolic dysregulation.[6-8] A recent study by Lee et al. found high physical activity inversely associated with MGUS, whereas heavy smoking and short sleep were positively associated with MGUS.[9] No approved treatments exist to prevent the progression of MGUS, but a recent pilot single-arm trial of a high-fiber dietary intervention in precursor plasma cell disorders demonstrated improvements in disease biomarkers and potential delays in progression to MM, underscoring growing interest in preventive strategies.[10]

Metabolic syndrome (MetS), characterized by a cluster of conditions including elevated fasting glucose, elevated blood pressure, elevated triglyceride levels, low HDL cholesterol levels, and obesity (particularly central adiposity), is a global public health concern, with a prevalence of 25-35% in developed countries, including South Korea.[11, 12] MetS is associated with increased risks of cardiovascular disease, all-cause mortality, and common cancers.[13, 14] Emerging evidence suggests that metabolic dysregulation may contribute to the pathogenesis of hematologic malignancies, potentially through chronic inflammation, oxidative stress, or

altered immune responses.[15] However, the association between MetS and MGUS remains poorly understood, with few large-scale studies exploring this relationship. This study aims to investigate the relationship between MetS and the risk of MGUS in a large Korean cohort, providing insights into the potential role of metabolic factors in the development of plasma cell disorders.

Methods

This retrospective cohort study used de-identified data from the Korean National Health Information Database (NHID), covering the entire population (>50 million).[16, 17] The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. X-2507-986-901); informed consent was waived.

Participants were adults aged ≥20 years who underwent National Health Insurance Service health checkups in 2012 (index year) and were followed until December 31, 2022. After excluding individuals with incomplete data, prior cancer/amyloidosis, or MGUS diagnosis within a 1-year lag period, 4,453,504 subjects were included (*Online Supplementary Figures S1*).

MetS was defined using modified NCEP-ATP III criteria requiring ≥3 of: central obesity (waist circumference ≥90 cm men/≥85 cm women), fasting glucose ≥100 mg/dL or treatment, blood pressure ≥130/85 mmHg or treatment, HDL-cholesterol <40 mg/dL men or <50 mg/dL women or treatment, and triglycerides ≥150 mg/dL or treatment.[18]

MGUS was defined as either (1) having ≥2 outpatient claims carrying the ICD-10 code D47.2 or (2) registration in the V193 rare/incurable disease financial assistance program.[19] Requiring ≥2 claims reduces false positives from rule-out coding, whereas V193 registration captures

confirmed cases with laboratory-supported diagnoses (typically serum/urine protein electrophoresis and immunofixation) who may have fewer subsequent claims.

Covariates (smoking, alcohol consumption, physical activity, income, and chronic kidney disease) were obtained from standardized questionnaires and laboratory measurements. For the longitudinal analysis, 3,294,672 individuals with ≥2 MetS assessments were classified into four groups based on changes in MetS status (No→No, No→Yes, Yes→No, Yes→Yes).

Incidence rates were calculated per 1,000 person-years. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals, with three levels of adjustment: Model 1 (crude), Model 2 (age- and sex-adjusted), Model 3 (additionally adjusted for smoking, alcohol, physical activity, income, and chronic kidney disease). Stratified analyses and interaction tests were performed by sex and age group. Detailed methods are provided in *Online Supplementary Appendix*.

Results

Patient characteristics

The cohort comprised 4,453,504 individuals, of whom 1,241 developed MGUS over a median follow-up of 9.3 years (range: 9.1–9.6 years). Table 1 summarizes the baseline characteristics of the cohort, revealing that individuals with MGUS (n=1,241) were older (mean age 61.3 vs. 48.1 years), more likely male (62.9% vs. 54.2%), and had higher rates of metabolic syndrome components, including hypertension (54.2% vs. 27.2%) and diabetes (23.3% vs. 9.9%), compared to those without MGUS (all $p < 0.0001$).

Association Between MetS and MGUS Incidence

Based on the Table 1, Cox proportional hazards models were used to assess the association between MetS and MGUS risk, adjusting for age, sex, income, smoking, alcohol consumption, physical activity, and chronic kidney disease (Model 3, Table 2). The analysis in Table 2 showed a significant positive association between MetS and increased MGUS risk. The IR of MGUS was 0.02 per 1,000 person-years for individuals without MetS and 0.05 per 1,000 PY for those with MetS. In Model 3, the HR was 1.28 (95% CI: 1.14–1.44). The risk of MGUS increased linearly with the number of MetS components (p-trend < 0.05). Compared to individuals with no MetS components (IR = 0.01 per 1,000 PY), those with five components had an IR of 0.08 per 1,000 PY and a 76% increased risk of MGUS (HR = 1.76, 95% CI: 1.35–2.30, Model 3). Among individual components, Low HDL Cholesterol (HR = 1.37, 95% CI: 1.22–1.54), High Blood Pressure (HR = 1.31, 95% CI: 1.16–1.49), and Central Obesity (HR = 1.18, 95% CI: 1.04–1.33) showed the strongest associations with MGUS. We further explored whether systolic blood pressure (SBP) or diastolic blood pressure (DBP) contributes differently to MGUS risk. To address this comment, we performed additional Cox proportional hazards analyses using baseline SBP and DBP, each categorized into quartiles (Q1: ≤25th percentile; Q2: >25th–50th percentile; Q3: >50th–75th percentile; Q4: >75th–100th percentile). When SBP was modeled in quartiles, the HRs relative to the lowest quartile (Q1) were 1.136 (95% CI, 0.949–1.361) for Q2, 1.122 (95% CI, 0.938–1.342) for Q3, and 1.212 (95% CI, 1.021–1.440) for Q4. When DBP was analyzed in quartiles, the HRs relative to Q1 were 0.864 (95% CI, 0.730–1.024) for Q2, 0.846 (95% CI, 0.713–1.003) for Q3, and 0.950 (95% CI, 0.805–1.122) for Q4. The cumulative incidence of MGUS in the MetS group rose steeply, while that in the non-MetS group increased more gradually during the observation period (p < 0.001)

(Figure 1A). Figure 1B revealed a dose-response relationship between the number of MetS components and the cumulative incidence of MGUS over the follow-up period ($p < 0.001$).

Sex- and Age-Specific Patterns

Subgroup analysis in Model 3 (adjusted for age, sex, income, smoking, alcohol consumption, regular physical activity, and chronic kidney disease) revealed significant associations between MetS and its components and the risk of MGUS, varying by sex and age *(Online Supplementary Table S1)*. For MetS, males had a higher MGUS risk than females, with a non-significant interaction p-value of 0.152. As the number of MetS components increased, males showed a consistently higher MGUS risk than females, particularly at MetS component counts of 4 and 5, although the interaction p-value was non-significant (0.073).

Age-specific analysis revealed a higher MGUS risk in the 20–39 age group compared to the 40–64 and ≥65 age groups, with a nearly significant interaction p-value of 0.053. The 20–39 age group exhibited the most pronounced MGUS risk with an increasing number of MetS components, supported by a significant interaction p-value ($p < 0.001$). Among individual components, Central Obesity showed a higher MGUS risk in males and the 20–39 age group ($p = 0.032$ and $p < 0.001$, respectively). High Blood Pressure showed an elevated MGUS risk in males and the 40–64 age group ($p = 0.014$), while Low HDL Cholesterol and Elevated Triglycerides had non-significant interactions across subgroups ($p > 0.05$). These findings indicate variations in MGUS risk associated with MetS and its components, with increasing sex differences as the number of MetS components rises and pronounced age-related patterns in younger individuals.

Impact of Longitudinal Changes in MetS Status

Longitudinal analysis in Table 3 showed that changes in MetS status and its components significantly increased the risk of MGUS. Development of MetS (No→Yes) had an IR of 0.05 per 1,000 PY and a HR of 1.25 (95% CI: 1.06–1.47, Model 3). Persistent MetS had a similar IR of 0.05 per 1,000 PY and an HR of 1.25 (95% CI: 1.06–1.48, Model 3), indicating increased MGUS risk with MetS onset or persistence. The MGUS risk for the resolution of MetS group (IR = 0.03 per 1,000 PY, HR = 1.00, 95% CI: 0.77–1.30) is not significantly different from the MGUS risk in the persistent absence of MetS group. Among components, transitions to High Blood Pressure (No→Yes; HR = 1.48, 95% CI: 1.23–1.78) and Low HDL Cholesterol (No→ Yes; HR = 1.47, 95% CI: 1.26–1.72) showed strong associations with increased MGUS risk. Persistent High Blood Pressure and Low HDL Cholesterol (Yes→Yes) also increased risk (HR = 1.32 and HR = 1.45, respectively). In contrast, changes in Elevated Glucose and Elevated Triglycerides showed weaker or non-significant associations, highlighting the predominant role of High Blood Pressure and Low HDL Cholesterol in MGUS risk.

Figure 2 illustrated the cumulative incidence of MGUS based on changes in MetS status. The persistent absence of MetS and resolution of MetS had the lowest cumulative incidence, while development of MetS and persistent MetS had higher cumulative incidence ($p < 0.001$). These findings indicate that MetS onset or persistence significantly increases MGUS risk, emphasizing the importance of preventing or reversing MetS to reduce MGUS risk.

Subgroup Differences in the Impact of MetS Changes

Subgroup analysis in *Online Supplementary Table S2*, based on Model 3, revealed varied

impacts of longitudinal changes in MetS and its components on MGUS risk by sex and age. For MetS, development of MetS (No→Yes) and persistent MetS (Yes→Yes) showed higher MGUS risks in males (HR = 1.43 and 1.39, respectively) than in females (HR = 0.97 and 1.03, respectively), with a non-significant interaction p-value of 0.106. The 20–39 age group exhibited the most pronounced risks (HR = 3.55 and 4.48, respectively), with a non-significant interaction p-value of 0.093. Central Obesity transitions (No→Yes and Yes→Yes) showed higher MGUS risks in males (HR = 1.24 and 1.36, respectively) and the 20–39 age group (HR = 3.10 and 4.55, respectively), with a significant age interaction (p = 0.006) and a nearly significant sex interaction (p = 0.087). High Blood Pressure transitions (No→Yes and Yes→Yes) showed higher MGUS risks in males (HR = 1.53 and 1.54, respectively) and the 40–64 age group (HR = 1.72 and 1.40, respectively), with nearly significant interactions for sex (p = 0.065) and age (p = 0.053). In contrast, Low HDL Cholesterol, Elevated Glucose, and Elevated Triglycerides showed non-significant interactions across subgroups, indicating minimal variation in MGUS risk by sex or age. These findings highlight the need for targeted prevention strategies, particularly for males and the 20–39 and 40–64 age groups.

Discussion

This study is the largest population-based cohort to date evaluating the association between MetS and its components and the risk of developing MGUS, a precursor to multiple myeloma. Our findings provide robust evidence that MetS was associated with increased MGUS risk, with patterns varying by sex, age, and longitudinal changes in metabolic health. While observational, our dose-response and longitudinal findings align with Bradford Hill criteria for

causality[20], warranting prospective validation.

Individuals with MetS had a 28% increased risk of developing MGUS compared to those without MetS, after adjustment for sociodemographic factors, lifestyle behaviors, and comorbidities such as chronic kidney disease. MGUS risk increased linearly with the number of MetS components, from an IR of 0.01 per 1,000 person-years with no components to 0.08 per 1,000 person-years with all five components. This dose-response relationship, with the highest risk in those with five components, supports a biological gradient consistent with potential causality.[20] These findings suggest that multifactorial metabolic dysregulation may contribute to MGUS pathogenesis. They align with prior research demonstrating that MetS induces chronic inflammatory states,[21, 22] which may promote monoclonal B-cell proliferation.[23, 24] Among MetS components, Low HDL Cholesterol, High Blood Pressure, and Central Obesity showed the strongest associations with MGUS risk, aligning with prior evidence linking chronic inflammation, further supported by elevated interleukin-6 and C-reactive protein levels in both MetS and MGUS patients.[25, 26] Post hoc quartile analysis of baseline blood pressure further revealed that SBP predominantly drove the association between hypertension and MGUS; individuals in the highest SBP quartile had a statistically significant 21% higher risk compared with those in the lowest quartile, whereas no clear linear association was observed for DBP. In contrast, Impaired Glucose Metabolism and Hypertriglyceridemia had weaker associations, indicating unequal contributions to MGUS development.

Subgroup analysis revealed significant sex and age differences in the MetS-MGUS association. Males consistently showed higher MGUS risk associated with MetS and its components compared to females, particularly as the number of MetS components increased. The 20–39 age group exhibited a markedly increased MGUS risk with accumulating MetS components, despite lower absolute incidence in this age range. This suggests that early onset

and clustering of metabolic risk factors in young adults may confer disproportionate risk for early plasma cell dyscrasias, highlighting the need for vigilant metabolic health management, particularly in men.[7, 27] Central Obesity and High Blood Pressure showed the most significant differential effects by sex and age. Central Obesity had a significant age interaction, with the highest risks in younger men, possibly reflecting unique metabolic and immunological consequences of early-life adiposity.[7, 27, 28] These findings underscore the need for tailored MGUS prevention and surveillance strategies, considering metabolic and demographic factors.

Longitudinal analyses showed that development of MetS or persistent MetS was associated with a 25% increased MGUS risk compared to persistent absence of MetS, whereas resolution of MetS normalized risk. Transitions to High Blood Pressure and Low HDL Cholesterol were the strongest predictors of increased MGUS risk, while changes in Elevated Glucose and Elevated Triglycerides had weaker or non-significant effects. These results highlight the dynamic nature of metabolic risk and its implications for plasma cell neoplasia, suggesting that improving metabolic health may reduce MGUS risk.[10, 14] Analysis of longitudinal changes by sex and age showed that the adverse effects of development of MetS or persistent MetS were most pronounced in males and younger individuals, particularly for Central Obesity and High Blood Pressure. Interaction analyses suggest that these groups may be especially susceptible to the hematologic consequences of metabolic dysfunction, emphasizing the need for aggressive risk factor modification. Early lifestyle modification and metabolic management, especially in high-risk groups such as younger males and those with multiple MetS components, may help prevent progression from subclinical plasma cell disorders to overt malignancy.

This study has several limitations. First, the definition of MGUS relied on administrative claims data (≥2 outpatient claims with ICD-10 code D47.2 or V193 registration), which are subject to potential diagnostic coding errors and do not provide direct laboratory confirmation

(e.g., serum and/or urine protein electrophoresis or immunofixation). Although requiring multiple claims and including V193 registration likely improves specificity and reduces misclassification compared with single-claim definitions, this approach remains vulnerable to coding errors, may omit mild or transient cases with only a single claim, and cannot fully exclude the possibility that a small proportion of cases had already progressed to smoldering or active multiple myeloma or other B-cell malignancies at the time of the initial D47.2 coding. Second, MGUS was detected incidentally during routine clinical practice rather than through systematic screening, which may introduce detection bias—individuals with MetS may undergo more frequent testing, potentially inflating the observed association.[29] Future studies with prospective serum protein electrophoresis–based screening could help mitigate this concern. Furthermore, the absence of detailed laboratory and bone marrow data precluded risk stratification of MGUS and direct assessment of whether MetS influences progression from MGUS to smoldering or active multiple myeloma beyond its association with MGUS incidence. We are conducting a follow-up study within the present NHID cohort to evaluate the 10-year risk of progression to multiple myeloma according to baseline and longitudinal MetS status, which may clarify whether MetS affects not only MGUS development but also subsequent disease evolution and aggressiveness. Third, despite adjustment for key covariates (age, sex, income, lifestyle factors, and chronic kidney disease), unmeasured confounders (e.g., family history, diet) may remain, and we could not fully account for chronic systemic inflammation or autoimmune disorders. Thus, we cannot exclude the possibility that part of the observed association is mediated through, or confounded by, unmeasured inflammatory pathways. Multiple imputation and sensitivity analyses suggest robustness, but residual bias cannot be fully excluded. Fourth, the generalizability of these findings to non-Asian populations requires further validation. Finally, although resolution of MetS was associated with a normalization of MGUS risk, we were unable to evaluate the cumulative duration of MetS in this cohort. We are

currently performing an additional analysis to examine the relationship between MetS duration and the probability of subsequent resolution; preliminary findings suggest that longer MetS duration is associated with a markedly lower likelihood of resolution. If confirmed, these findings would suggest that prolonged metabolic dysfunction represents a less modifiable state that sustains elevated MGUS risk over time, underscoring the importance of early and aggressive metabolic intervention to prevent both the onset and chronicity of MetS.

In conclusion, MetS and its key components, particularly when persistent or accumulating, were significantly associated with MGUS risk. This risk is most pronounced in younger adults and males, with Central Obesity and High Blood Pressure playing prominent roles. Preventing and managing MetS may reduce MGUS incidence and the burden of multiple myeloma and related disorders.

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Table 1. Baseline characteristics of cohort

	Total (n = 4,453,504)	MGUS		
		No (n = 4,452,263)	Yes (n = 1,241)	p
Age groups, years, mean ± SD	48.1 ± 13.8	48.1 ± 13.8	61.3 ± 11.3	<.0001
20-39	1,245,176 (28.0)	1,245,132 (28.0)	44 (3.6)	<.0001
40-64	2,637,788 (59.2)	2,637,113 (59.2)	675 (54.4)	
≥ 65	570,540 (12.8)	570,018 (12.8)	522 (42.1)	
Sex, N (%)				<.0001
Male	2,413,277 (54.2)	2,412,496 (54.2)	781 (62.9)	
Female	2,040,227 (45.8)	2,039,767 (45.8)	460 (37.1)	
Income, Low, N (%)	831,475 (18.7)	831,223 (18.7)	252 (20.3)	0.1391
Smoking, N (%)				<.0001
Never	2,655,206 (59.6)	2,654,510 (59.6)	696 (56.1)	
Ex or current	1,798,298 (40.4)	1,797,753 (40.4)	545 (43.9)	
Drinking, N (%)				<.0001
Non	2,255,387 (50.6)	2,254,630 (50.6)	757 (61.0)	
Mild/heavy	2,198,117 (49.4)	2,197,633 (49.4)	484 (39.0)	
Physical activity_regular exercise, N (%)	845,926 (19.0)	845,626 (19.0)	300 (24.2)	<.0001
Body mass index, kg/m^2, mean ± SD	23.8 ± 3.3	23.8 ± 3.3	24.2 ± 3.13	<.0001
WC ≥ 90 cm for men, or ≥ 85 cm for women, N (%)	894,035 (20.1)	893,666 (20.1)	369 (29.7)	<.0001
Diabetes mellitus, N (%)	441,377 (9.9)	441,088 (9.9)	289 (23.3)	
Hypertension, N (%)	1,211,238 (27.2)	1,210,565 (27.2)	673 (54.2)	
Fasting glucose, mg/dL, mean ± SD	97.8 ± 23.2	97.8 ± 23.2	104.8 ± 29.4	<.0001
Systolic blood pressure, mmHg, mean ± SD	121.9 ± 14.8	121.9 ± 14.8	126.8 ± 15.2	<.0001
Diastolic blood pressure, mmHg, mean ± SD	76.2 ± 10.0	76.1 ± 10.0	77.4 ± 10.3	<.0001

High-density lipoprotein, mg/dL, mean ± SD	55.5 ± 17.6	55.5 ± 17.6	51.2 ± 13.4	<.0001
Triglyceride[a], mg/dL	109.6 (109.5-109.6)	109.6 (109.5-109.6)	114.5 (111.1-118.0)	0.0062
Chronic kidney disease, N (%)	115,474 (2.6)	115,311 (2.6)	163 (13.1)	<.0001
Estimated GFR, mL/min/1.73m^2, mean ± SD	95.2 ± 17.6	95.2 ± 17.6	82.9 ± 20.4	<.0001
Proteinuria, N (%)	96,836 (2.2)	96,726 (2.2)	110 (8.9)	<.0001

Regular exercise was defined as moderate-intensity activity performed for at least 30 minutes, five or more times per week, or high-intensity activity performed for at least 20 minutes, three or more times per week. Low income was defined as being in the lowest income group (within the bottom 25% of the income distribution) or meeting the criteria for medical aid benefits. SD, standard deviation; WC, waist circumference; GFR, Glomerular filtration rate

[a]Geometric mean (95% confidence interval)

Table 2. Incidence Rates of Monoclonal Gammopathy of Undetermined Significance by Metabolic Syndrome Status and Components

						Hazard ratio (95% CI)		
		N	MGUS	Person years	IR*	Model 1	Model 2	Model 3
MetS	No	3,270,586	664	30,233,962	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1,182,918	577	10,742,490	0.05	2.46 (2.20-2.75)	1.34 (1.19-1.50)	1.28 (1.14-1.44)
Number of MetS Components	0	1,204,983	137	11,217,415	0.01	1 (Ref.)	1 (Ref.)	1 (Ref.)
	1	1,160,392	247	10,719,705	0.02	1.89 (1.53-2.33)	1.17 (0.95-1.44)	1.18 (0.95-1.45)
	2	905,211	280	8,296,841	0.03	2.77 (2.26-3.40)	1.30 (1.06-1.60)	1.31 (1.06-1.61)
	3	642,541	267	5,861,978	0.05	3.75 (3.05-4.61)	1.48 (1.2-1.83)	1.46 (1.18-1.81)
	4	39,6390	210	3,586,313	0.06	4.83 (3.90-5.99)	1.60 (1.28-2.00)	1.53 (1.22-1.92)
	5	14,3987	100	1,294,200	0.08	6.39 (4.94-8.27)	1.89 (1.45-2.47)	1.76 (1.35-2.30)
Central obesity†	No	3,559,469	872	32,803,909	0.03	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	894,035	369	8,172,544	0.05	1.70 (1.51-1.92)	1.20 (1.06-1.36)	1.18 (1.04-1.33)
Elevated glucose†	No	3,010,658	664	27,868,340	0.02	1 (Ref.)	1(Ref.)	1 (Ref.)
	Yes	1,442,846	577	13,108,112	0.04	1.86 (1.66-2.08)	1.13 (1.01-1.26)	1.10 (0.98-1.24)
Hypertension†	No	2,472,598	389	22,957,232	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1,980,906	852	18,019,221	0.05	2.81 (2.49-3.16)	1.34 (1.18-1.52)	1.31 (1.16-1.49)
Low HDL cholesterol†	No	3,123,252	659	28,815,099	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1,330,252	582	12,161,354	0.05	2.09 (1.87-2.34)	1.43 (1.28-1.61)	1.37 (1.22-1.54)
Elevated triglycerides†	No	2,897,611	673	26,722,113	0.03	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1,555,893	568	14,254,340	0.04	1.59 (1.42-1.77)	1.11 (0.99-1.24)	1.07 (0.96-1.20)

MGUS, monoclonal gammopathy of undetermined significance; IR, incidence rate; 95% CI, 95% confidence interval; MetS, metabolic syndrome; HDL, high-density lipoprotein

†Full criteria (NCEP-ATP III): waist circumference ≥ 90 cm (men) or ≥ 85 cm (women); fasting glucose ≥ 100 mg/dL or use of antidiabetic medication; blood pressure ≥ 130/85 mmHg or use of antihypertensive medication; HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women) or drug treatment for low HDL cholesterol; (5) triglycerides

≥ 150 mg/dL or drug treatment for elevated triglycerides.

*Incidence per 1000 person years.

Model 1: Non-adjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, smoking, alcohol consumption, and household income, physical activity, chronic kidney disease

Table 3. Incidence Rates and Hazard Ratios of Monoclonal Gammopathy of Undetermined Significance by Longitudinal Changes in Metabolic Syndrome Status and Components

						Hazard ratio (95% CI)		
		N	MGUS	Person years	IR*	Model 1	Model 2	Model 3
MetS	No→No	2,193,682	451	2,032,4378	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	No→Yes	477,108	230	4,357,078	0.05	2.39 (2.04-2.80)	1.29 (1.10-1.52)	1.25 (1.06-1.47)
	Yes→No	210,354	64	1,931,478	0.03	1.50 (1.15-1.95)	1.01 (0.77-1.31)	1.00 (0.77-1.30)
	Yes→Yes	413,532	205	3,761,300	0.05	2.47 (2.10-2.92)	1.31 (1.11-1.55)	1.25 (1.05-1.48)
Central obesity†	No→No	2,428,708	600	22,440,693	0.03	1 (Ref.)	1 (Ref.)	1 (Ref.)
	No→Yes	229,768	81	2,110,287	0.04	1.44 (1.14-1.82)	1.07 (0.85-1.35)	1.06 (0.84-1.33)
	Yes→No	207,641	75	1,901,399	0.04	1.48 (1.16-1.88)	0.99 (0.78-1.26)	0.97 (0.77-1.24)
	Yes→Yes	428,559	194	3,921,855	0.05	1.86 (1.58-2.18)	1.23 (1.05-1.45)	1.20 (1.02-1.41)
Elevated glucose†	No→No	1,854,175	412	17,203,564	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	No→Yes	455,661	153	4,173,859	0.04	1.54 (1.28-1.85)	1.05 (0.87-1.26)	1.03 (0.85-1.24)
	Yes→No	364,275	102	3,360,828	0.03	1.27 (1.02-1.58)	0.95 (0.76-1.18)	0.95 (0.76-1.18)
	Yes→Yes	620,565	283	5,635,984	0.05	2.11 (1.82-2.46)	1.13 (0.97-1.32)	1.11 (0.95-1.29)
Hypertension†	No→No	1,462,566	215	13,609,111	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	No→Yes	614,989	270	5,629,415	0.05	3.05 (2.55-3.65)	1.51 (1.25-1.82)	1.48 (1.23-1.78)
	Yes→No	338,108	76	3,128,887	0.02	1.54 (1.19-2.00)	1.11 (0.85-1.44)	1.12 (0.86-1.45)
	Yes→Yes	879,013	389	8,006,821	0.05	3.10 (2.62-3.66)	1.35 (1.13-1.61)	1.32 (1.11-1.58)
Low HDL cholesterol†	No→No	2,029,974	422	18,761,992	0.02	1 (Ref.)	1 (Ref.)	1 (Ref.)
	No→Yes	544,043	263	4,987,929	0.05	2.35 (2.01-2.74)	1.52 (1.30-1.78)	1.47 (1.26-1.72)
	Yes→No	272,433	74	2,509,883	0.03	1.31 (1.03-1.68)	1.16 (0.90-1.48)	1.13 (0.88-1.45)
	Yes→Yes	448,226	191	4,114,430	0.05	2.07 (1.74-2.45)	1.52 (1.27-1.82)	1.45 (1.21-1.74)
Elevated triglycerides†	No→No	1,794,856	426	16,592,804	0.03	1 (Ref.)	1 (Ref.)	1 (Ref.)

No→Yes	529,558	223	4,861,154	0.05	1.79 (1.52-2.10)	1.16 (0.99-1.37)	1.13 (0.96-1.33)
Yes→No	315,875	90	2,906,632	0.03	1.21 (0.96-1.52)	0.94 (0.75-1.18)	0.94 (0.75-1.18)
Yes→Yes	654,387	211	6,013,644	0.04	1.37 (1.16-1.62)	1.01 (0.85-1.19)	0.98 (0.83-1.15)

MGUS, monoclonal gammopathy of undetermined significance; IR, incidence rate; 95% CI, 95% confidence interval; MetS, metabolic syndrome; HLD, high-density lipoprotein

†Full criteria (NCEP-ATP III): waist circumference ≥ 90 cm (men) or ≥ 85 cm (women); fasting glucose ≥ 100 mg/dL or use of antidiabetic medication; blood pressure ≥ 130/85 mmHg or use of antihypertensive medication; HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women) or drug treatment for low HDL cholesterol; (5) triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides.

*Incidence per 1000 person years.

Model 1: Non-adjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, smoking, alcohol consumption, and household income, physical activity, chronic kidney disease

Figure legends

Figure 1. Kaplan-Meier curves showing the cumulative incidence probability of MGUS according to metabolic syndrome status.

(A) Comparison of MGUS incidence between individuals with metabolic syndrome and those without metabolic syndrome.
(B) Cumulative incidence probability of MGUS stratified by the number of metabolic syndrome components (0 to 5).

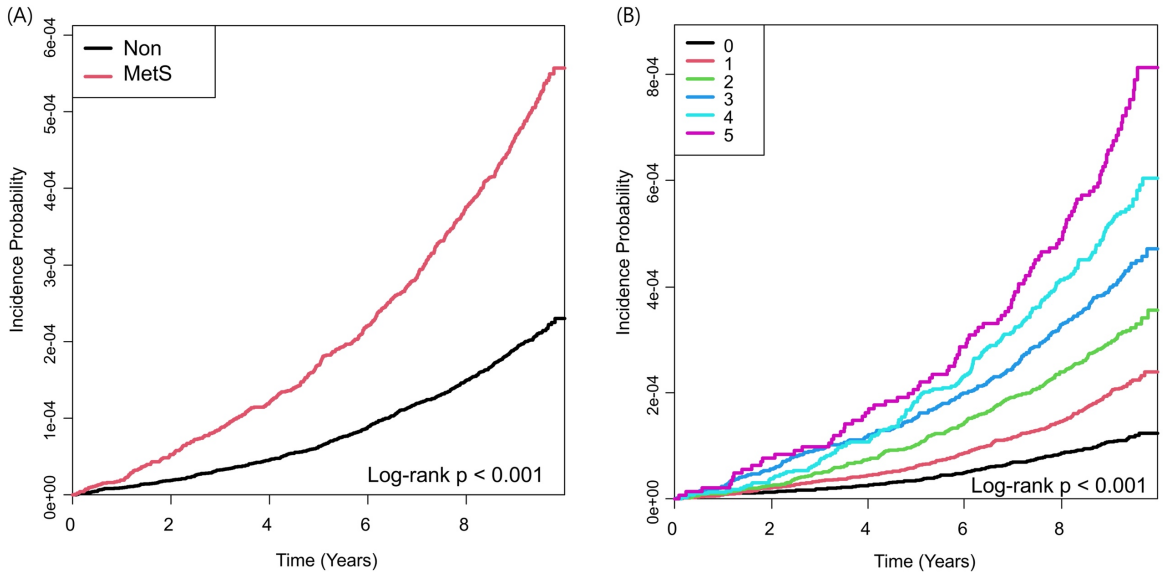
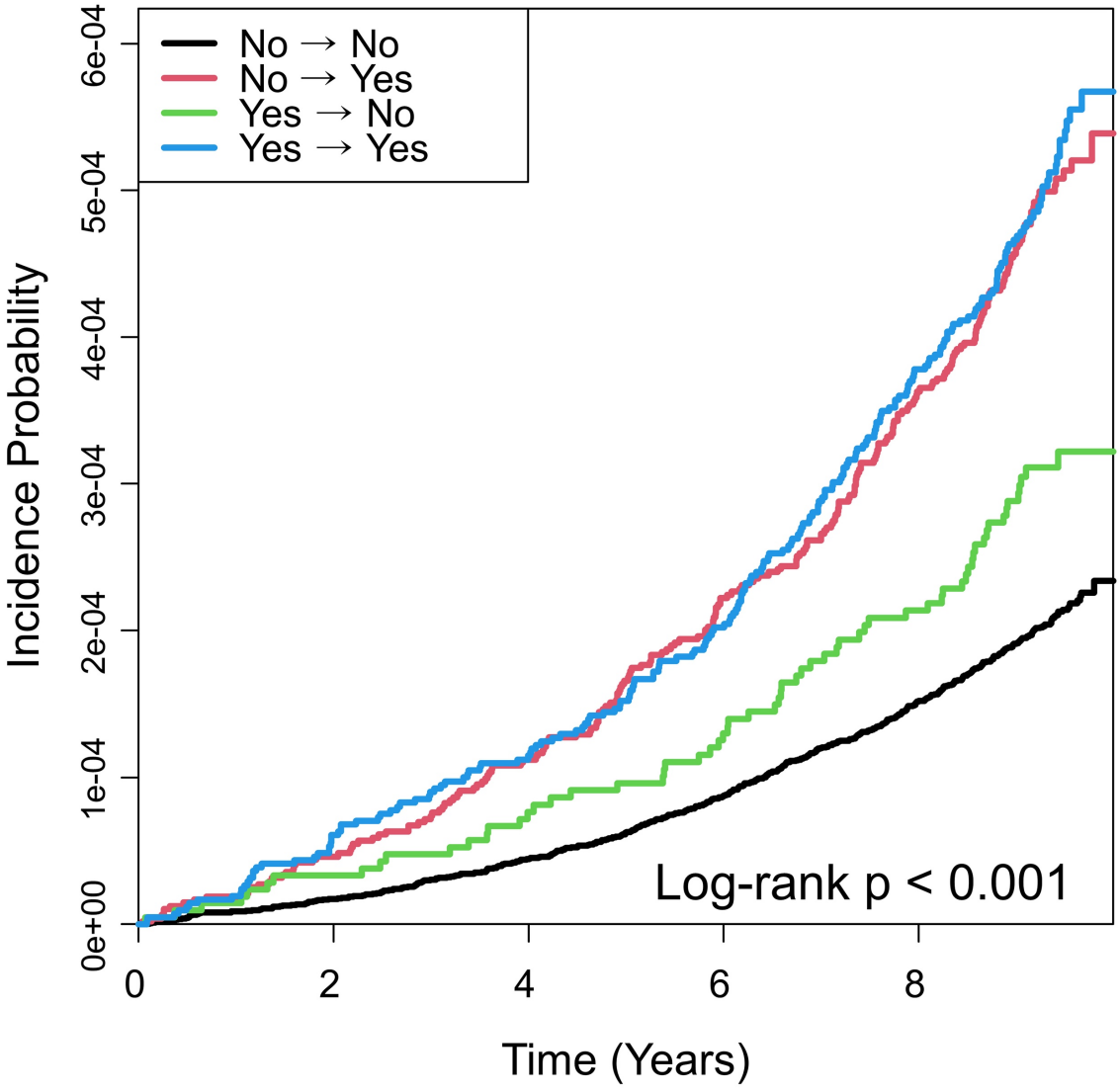


Figure 2. Kaplan-Meier curves showing the cumulative incidence probability of MGUS by metabolic syndrome Status Transitions.



Supplementary methods

Study Design

This retrospective cohort study utilized data from the National Health Information Database (NHID), a comprehensive public health big data platform established and maintained by the National Health Insurance Service (NHIS). The NHID covers South Korea's entire population of over 50 million individuals.[16] The NHIS oversees South Korea's national health insurance system, reimbursing healthcare providers and pharmacies based on submitted claims.[17] he NHIS also conducts biennial health examinations for all employees, regardless of age, and for adults aged 40 years or older. These health checkups include anthropometric measurements, laboratory assessments (e.g., lipid profiles and blood glucose), and standardized questionnaires on lifestyle factors, such as smoking, alcohol use, and physical activity.[16]

The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. X-2507-986-901). The requirement for informed consent was waived because the data were publicly available and de-identified prior to analysis.

Study Population

The enrollment process for the study cohort is illustrated in *Online Supplementary Figures S1*. We included individuals who underwent NHIS health checkups between January 1, 2012, and December 31, 2012 (index year), and followed them until December 31, 2022, to identify new cases of MGUS. The cohort included 4,910,068 adults who completed NHIS health checkups in 2012, representing 40% of the eligible workplace/regional insurance adults aged ≥ 20 years. The exclusion criteria were as follows: individuals with incomplete data (e.g., misentered

questionnaire responses or aberrant lab values, n = 333,385), those with a prior diagnosis of cancer or amyloidosis before the index date (n = 112,700), and those diagnosed with MGUS within the 1-year lag period (n = 65). Therefore, 4,453,504 individuals were included in the study population.

Definition of Metabolic Syndrome and MGUS

MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria.[18] It required at least three of the following: (1) waist circumference ≥ 90 cm (men) or ≥ 85 cm (women); (2) fasting glucose ≥ 100 mg/dL or use of antidiabetic medication; (3) blood pressure ≥ 130/85 mmHg or use of antihypertensive medication; (4) HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women) or drug treatment for low HDL cholesterol; (5) triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides.

MGUS cases were defined as individuals with at least two outpatient visits coded as MGUS (International Classification of Diseases [ICD-10] code D47.2) or registered under the V193 code (a special copayment reduction program for cancer patients in South Korea). This definition was chosen to enhance diagnostic specificity in claims data. Multiple outpatient visits minimize misclassification, and V193 registration reflects confirmed diagnoses, typically supported by laboratory evidence such as serum protein electrophoresis.[19] MGUS cases were incidentally diagnosed in clinical practice (e.g., during workups for comorbidities) rather than through a formal national screening program, which may introduce acquisition bias.

Data Collection and Covariates

A standardized self-administered questionnaire was used to collect data on smoking status, alcohol consumption, and physical activity. Regular exercise was defined as moderate-intensity activity performed for at least 30 minutes, five or more times per week, or high-intensity activity performed for at least 20 minutes, three or more times per week. Low income was defined as being in the lowest income group (within the bottom 25% of the income distribution) or meeting the criteria for medical aid benefits.

For the longitudinal analysis of changes in MetS status and MGUS risk, 3,294,672 individuals who underwent both baseline and follow-up MetS assessments were included from the baseline cohort. These individuals were categorized into four groups based on MetS status changes: persistent absence of MetS (No→No), development of MetS (No→Yes), resolution of MetS (Yes→No), and persistent MetS (Yes→Yes). The study evaluated MGUS risk associated with MetS status changes, calculating hazard ratios using models adjusted for relevant covariates to assess the impact of MetS changes on MGUS incidence over time.

Statistical Analysis

Statistical analyses evaluated baseline characteristics, incidence rates, and associations between MetS status changes and MGUS risk. Categorical variables were summarized with frequencies/percentages and continuous variables with means ± SDs; comparisons used chi-square and t-tests, respectively. The large cohort size yielded significant differences in most variables by MGUS status. Incidence rates (IRs) were computed as MGUS cases per 1,000 person-years, with group differences assessed. Cox proportional hazards models estimated HRs and 95% CIs for MGUS risk by MetS changes (reference: No→No): Model 1 (unadjusted), Model 2 (age/sex-adjusted), Model 3 (further adjusted for smoking, alcohol, physical activity,

income, CKD). Robustness was evaluated via stratified Cox models by sex and age (20–39, 40–64, ≥65 years), including interaction p-values. Analyses used SAS 9.3; two-sided $p<0.05$ significant.

Supplementary Table S1. Association of Metabolic Syndrome and Its Components with Monoclonal Gammopathy of Undetermined Significance: A Subgroup Analysis by Sex and Age

		Hazard ratio (95% CI) for Subgroup (Model 3)						
		Male	Female	p inter	Age 20-39	Age 40-64	Age ≥ 65	p inter
MetS	No	1 (Ref.)	1 (Ref.)	0.152	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.053
	Yes	1.36 (1.18-1.57)	1.15 (0.95-1.39)		2.73 (1.447,5.156)	1.29 (1.10-1.50)	1.21 (1.01-1.44)	
Number of MetS Components	0	1 (Ref.)	1 (Ref.)	0.073	1 (Ref.)	1 (Ref.)	1 (Ref.)	< 0.001
	1	1.33 (1.01-1.76)	1.00 (0.73-1.39)		0.77 (0.34-1.77)	1.40 (1.08-1.82)	0.76 (0.52-1.13)	
	2	1.45 (1.10-1.91)	1.15 (0.84-1.58)		0.84 (0.32-2.16)	1.5 (1.15-1.96)	0.89 (0.61-1.29)	
	3	1.57 (1.19-2.09)	1.34 (0.98-1.84)		1.04 (0.35-3.15)	1.49 (1.13-1.97)	1.11 (0.77-1.60)	
	4	1.94 (1.45-2.60)	1.06 (0.75-1.50)		5.82 (2.54-13.32)	1.83 (1.36-2.46)	0.93 (0.64-1.36)	
	5	2.20 (1.55-3.10)	1.29 (0.86-1.94)		2.81 (0.37-21.31)	2.32 (1.61-3.34)	1.06 (0.69-1.62)	
Central obesity†	No	1 (Ref.)	1 (Ref.)	0.032	1 (Ref.)	1 (Ref.)	1 (Ref.)	< 0.001
	Yes	1.30 (1.12-1.52)	0.98 (0.80-1.21)		3.10 (1.69-5.68)	1.32 (1.11-1.56)	0.97 (0.80-1.16)	
Elevated glucose†	No	1 (Ref.)	1 (Ref.)	0.073	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.281
	Yes	1.19 (1.03,1.37)	0.96 (0.79-1.16)		1.82 (0.96-3.43)	1.07 (0.92-1.25)	1.08 (0.91-1.29)	
Hypertension†	No	1 (Ref.)	1 (Ref.)	0.051	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.014
	Yes	1.44 (1.30-1.69)	1.13 (0.93-1.38)		1.71 (0.94-3.11)	1.48 (1.26-1.73)	1.02 (0.82-1.26)	
Low HDL cholesterol†	No	1 (Ref.)	1 (Ref.)	0.271	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.317
	Yes	1.44 (1.25-1.67)	1.27 (1.05-1.53)		1.43 (0.71-2.89)	1.48 (1.27,1.72)	1.24 (1.04-1.47)	
Elevated triglycerides†	No	1 (Ref.)	1 (Ref.)	0.959	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.735
	Yes	1.07 (0.93-1.23)	1.08 (0.89-1.30)		1.08 (0.57-2.05)	1.02 (0.88-1.19)	1.12 (0.94-1.33)	

95% CI, 95% confidence interval; MetS, metabolic syndrome; p inter, p-values for interaction between the covariate (MetS status) and subgroup (sex or age); HLD, high-density lipoprotein

†Full criteria (NCEP-ATP III): waist circumference ≥ 90 cm (men) or ≥ 85 cm (women); fasting glucose ≥ 100 mg/dL or use of antidiabetic medication; blood pressure ≥

130/85 mmHg or use of antihypertensive medication; HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women) or drug treatment for low HDL cholesterol; (5) triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides.

Model 3: Adjusted for age, sex, smoking, alcohol consumption, and household income, physical activity, chronic kidney disease

Supplementary Table S2. Monoclonal Gammopathy of Undetermined Significance by Longitudinal Changes in Metabolic Syndrome and Its Components Across Sex and Age Subgroups (Model 3)

		Hazard ratio (95% CI) for Subgroup (Model 3)						
		Male	Female	p inter	Age 20-39	Age 40-64	Age ≥ 65	p inter
MetS	No→No	1 (Ref.)	1 (Ref.)	0.106	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.093
	No→Yes	1.43 (1.17-1.75)	0.97 (0.74-1.28)		3.55 (1.40-9.00)	1.21 (0.96-1.51)	1.21 (0.95-1.54)	
	Yes→No	1.06 (0.77-1.46)	0.88 (0.56-1.41)		1.58 (0.37-6.84)	0.91 (0.63-1.31)	1.06 (0.71-1.56)	
	Yes→Yes	1.39 (1.13-1.71)	1.03 (0.78-1.36)		4.48 (1.85-10.80)	1.21 (0.95-1.53)	1.19 (0.93-1.53)	
Central obesity†	No→No	1 (Ref.)	1 (Ref.)	0.087	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.006
	No→Yes	1.24 (0.94-1.65)	0.79 (0.52-1.18)		3.10 (1.04-9.20)	1.13 (0.82-1.56)	0.89 (0.63-1.28)	
	Yes→No	1.06 (0.79-1.44)	0.83 (0.56-1.25)		0.00 (0.00-2.33)	0.88 (0.61-1.28)	1.05 (0.76-1.45)	
	Yes→Yes	1.36 (1.11-1.66)	0.95 (0.72-1.26)		4.55 (2.13-9.72)	1.34 (1.07-1.69)	0.97 (0.76-1.25)	
Elevated glucose†	No→No	1 (Ref.)	1 (Ref.)	0.265	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.491
	No→Yes	1.17 (0.93-1.47)	0.81 (0.58-1.12)		2.14 (0.84-5.47)	0.97 (0.75-1.25)	1.02 (0.77-1.36)	
	Yes→No	1.00 (0.76-1.31)	0.90 (0.62-1.29)		2.04 (0.75-5.58)	0.90 (0.67-1.20)	0.93 (0.66-1.32)	
	Yes→Yes	1.198(0.99-1.45)	0.97 (0.74-1.26)		2.44 (0.89-6.66)	1.02 (0.82-1.26)	1.13 (0.90-1.43)	
Hypertension†	No→No	1 (Ref.)	1 (Ref.)	0.065	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.053
	No→Yes	1.53 (1.21-1.95)	1.41 (1.07-1.88)		1.83 (0.40-4.82)	1.72 (1.36-2.16)	1.09 (0.79-1.50)	
	Yes→No	1.16 (0.83-1.61)	1.09 (0.70-1.70)		0.65 (0.15-2.87)	1.05 (0.74-1.48)	1.20 (0.78-1.85)	
	Yes→Yes	1.54 (1.23-1.92)	1.01 (0.76,1.34)		2.66 (1.19-5.95)	1.40 (1.12-1.75)	1.07 (0.79-1.44)	
Low HDL cholesterol†	No→No	1 (Ref.)	1 (Ref.)	0.137	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.396
	No→Yes	1.62 (1.34-1.95)	1.20 (0.91-1.60)		2.82 (1.20-6.62)	1.51 (1.22-1.87)	1.34 (1.06-1.70)	
	Yes→No	0.98 (0.69-1.39)	1.28 (0.89-1.85)		1.47 (0.44-4.91)	1.29 (0.94-1.78)	0.90 (0.60-1.36)	
	Yes→Yes	1.50 (1.18-1.91)	1.35 (1.03-1.76)		0.43 (0.06-3.22)	1.53 (1.20-1.95)	1.37 (1.05-1.77)	
Elevated triglycerides†	No→No	1 (Ref.)	1 (Ref.)	0.502	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.711

No→Yes	1.20 (0.97-1.48)	1.03 (0.79-1.34)	0.92 (0.27-3.15)	1.16 (0.92-1.45)	1.10 (0.87-1.40)
Yes→No	1.05 (0.80-1.37)	0.73 (0.47-1.12)	1.46 (0.49-4.37)	0.95 (0.70-1.29)	0.87 (0.60-1.25)
Yes→Yes	1.02 (0.83-1.25)	0.91 (0.68-1.22)	1.69 (0.75-3.83)	0.89 (0.71-1.12)	1.02 (0.79-1.31)

95% CI, 95% confidence interval; MetS, metabolic syndrome; p inter, p-values for interaction between the covariate (MetS status) and subgroup (sex or age); HLD, high-density lipoprotein

†Full criteria (NCEP-ATP III): waist circumference ≥ 90 cm (men) or ≥ 85 cm (women); fasting glucose ≥ 100 mg/dL or use of antidiabetic medication; blood pressure ≥ 130/85 mmHg or use of antihypertensive medication; HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women) or drug treatment for low HDL cholesterol; (5) triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides.

Model 3: Adjusted for age, sex, smoking, alcohol consumption, and household income, physical activity, chronic kidney disease

Supplementary Figure S1. Flowchart showing the enrollment process for the study cohort.