

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

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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 up to 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 (hazard ratio [HR]=1.28; 95% confidence interval [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 high-density lipoprotein cholesterol, hypertension, and central obesity were key risk factors, with higher risks in males and younger adults (range, 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.

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 high-density lipoprotein (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 (number 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 $\geq 130/85$ 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 (i) having ≥ 2 outpatient claims carrying the ICD-10 code D47.2 or (ii) registration in the V193 rare/incurable disease financial assistance program.¹⁹

Table 1. Baseline characteristics of cohort.

Characteristics	Total N=4,453,504	MGUS		
		No N=4,452,263	Yes N=1,241	P
Age groups, years, mean \pm SD	48.1 \pm 13.8	48.1 \pm 13.8	61.3 \pm 11.3	<0.0001
20-39, N (%)	1,245,176 (28.0)	1,245,132 (28.0)	44 (3.6)	<0.0001
40-64, N (%)	2,637,788 (59.2)	2,637,113 (59.2)	675 (54.4)	
≥ 65 , N (%)	570,540 (12.8)	570,018 (12.8)	522 (42.1)	
Sex, N (%)				<0.0001
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 (%)				<0.0001
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 (%)				<0.0001
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)	<0.0001
Body mass index, kg/m ² , mean \pm SD	23.8 \pm 3.3	23.8 \pm 3.3	24.2 \pm 3.13	<0.0001
WC ≥ 90 cm for men, or ≥ 85 cm for women, N (%)	894,035 (20.1)	893,666 (20.1)	369 (29.7)	<0.0001
Diabetes mellitus, N (%)	441,377 (9.9)	441,088 (9.9)	289 (23.3)	<0.0001
Hypertension, N (%)	1,211,238 (27.2)	1,210,565 (27.2)	673 (54.2)	<0.0001
Fasting glucose, mg/dL, mean \pm SD	97.8 \pm 23.2	97.8 \pm 23.2	104.8 \pm 29.4	<0.0001
Systolic blood pressure, mmHg, mean \pm SD	121.9 \pm 14.8	121.9 \pm 14.8	126.8 \pm 15.2	<0.0001
Diastolic blood pressure, mmHg, mean \pm SD	76.2 \pm 10.0	76.1 \pm 10.0	77.4 \pm 10.3	<0.0001
High-density lipoprotein, mg/dL, mean \pm SD	55.5 \pm 17.6	55.5 \pm 17.6	51.2 \pm 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)	<0.0001
Estimated GFR, mL/min/1.73m ² , mean \pm SD	95.2 \pm 17.6	95.2 \pm 17.6	82.9 \pm 20.4	<0.0001
Proteinuria, N (%)	96,836 (2.2)	96,726 (2.2)	110 (8.9)	<0.0001

Regular exercise was defined as moderate-intensity activity performed for at least 30 minutes, 5 or more times per week, or high-intensity activity performed for at least 20 minutes, 3 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. ^aGeometric mean (95% confidence interval)

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 \rightarrow No, No \rightarrow Yes, Yes \rightarrow No, Yes \rightarrow Yes). Incidence rates were calculated per 1,000 person-years. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI), 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 the *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 metabolic syndrome and monoclonal gammopathy of undetermined significance 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

Table 2. Incidence rates of monoclonal gammopathy of undetermined significance by metabolic syndrome status and components.

	N	MGUS	Person years	IR*	Hazard ratio (95% CI)		
					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)

[†]Full criteria (NCEP-ATP III): waist circumference ≥ 90 cm (men) or ≥ 85 cm (women); fasting glucose ≥ 100 mg/dL or use of anti-diabetic medication; blood pressure $\geq 130/85$ mmHg or use of anti-hypertensive medication; high-density lipoprotein (HDL) cholesterol < 40 mg/dL (men) or < 50 mg/dL (women) or drug treatment for low HDL cholesterol; triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides. *Incidence per 1,000 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. MGUS: monoclonal gammopathy of undetermined significance; IR: incidence rate; CI: confidence interval; MetS: metabolic syndrome; Ref: reference.

(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 (incidence rate [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) differentially contribute to MGUS risk. We performed additional Cox proportional hazards analyses using baseline SBP and DBP, each categorized into quartiles (Q1: $\leq 25^{\text{th}}$ percentile; Q2: $>25^{\text{th}}-50^{\text{th}}$ percentile; Q3: $>50^{\text{th}}-75^{\text{th}}$ percentile; Q4: $>75^{\text{th}}-100^{\text{th}}$ percentile). When SBP was modeled in quartiles, the HR 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 HR 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

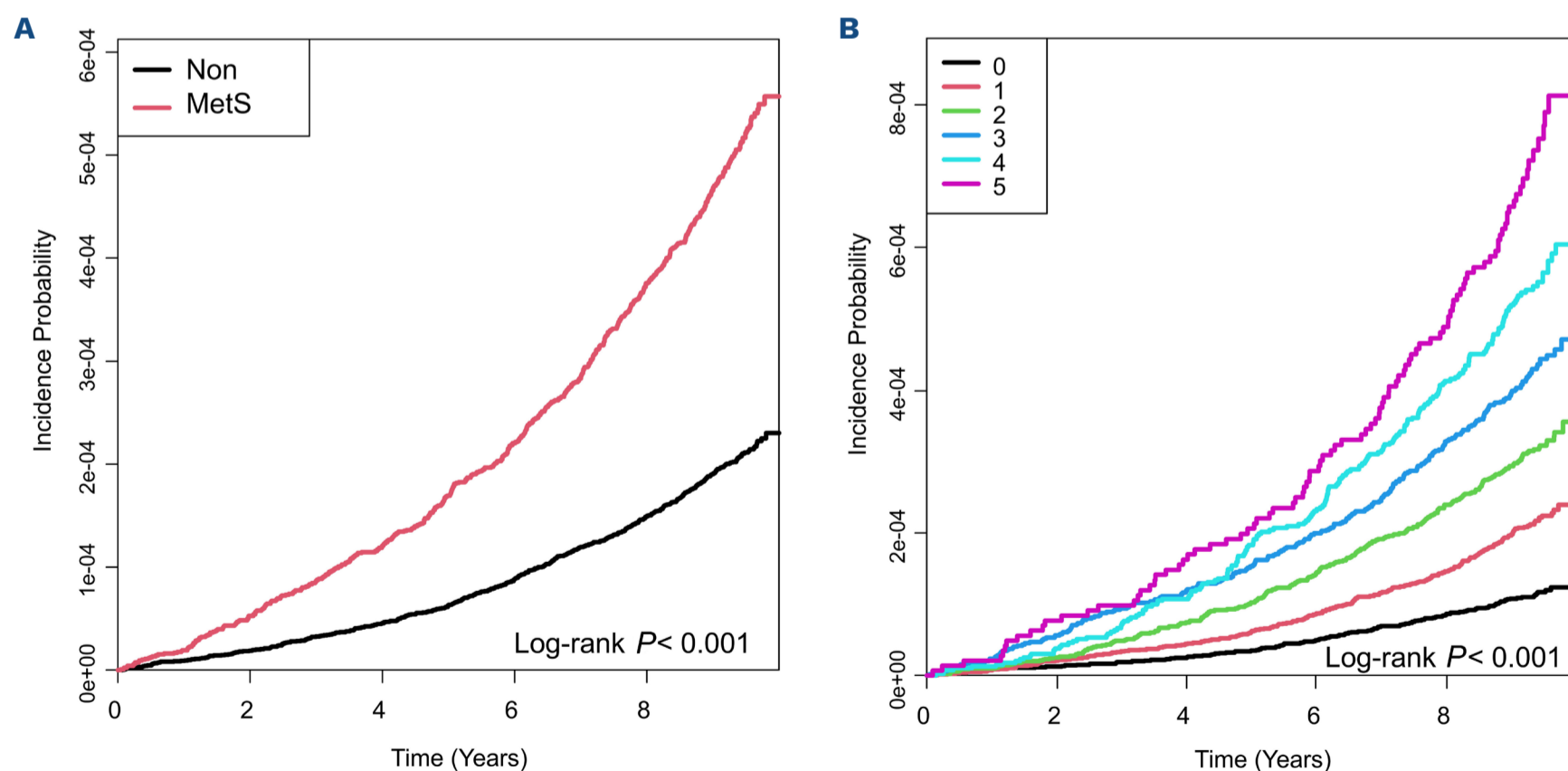


Figure 1. Kaplan-Meier curves showing the cumulative incidence probability of monoclonal gammopathy of undetermined significance according to metabolic syndrome status. (A) Comparison of monoclonal gammopathy of undetermined significance (MGUS) incidence between individuals with metabolic syndrome and those without metabolic syndrome (MetS). (B) Cumulative incidence probability of MGUS stratified by the number of MetS components (0 to 5).

as the number of MetS components rises and pronounced age-related patterns in younger individuals.

Impact of longitudinal changes in metabolic syndrome 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 illustrates the cumulative incidence of MGUS based on changes in MetS status. The persistent absence of MetS and resolution of MetS had the lowest cumulative

Table 3. Incidence rates and hazard ratios of monoclonal gammopathy of undetermined significance by longitudinal changes in metabolic syndrome status and components.

	N	MGUS	Person years	IR*	Hazard ratio (95% CI)		
					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)

[†]Full criteria (NCEP-ATP III): waist circumference ≥90 cm (men) or ≥85 cm (women); fasting glucose ≥100 mg/dL or use of anti-diabetic medication; blood pressure ≥ 130/85 mmHg or use of anti-hypertensive medication; high-density lipoprotein (HDL) cholesterol <40 mg/dL (men) or <50 mg/dL (women) or drug treatment for low HDL cholesterol; triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides. *Incidence per 1,000 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. MGUS: monoclonal gammopathy of undetermined significance; IR: incidence rate; CI: confidence interval; MetS: metabolic syndrome; Ref: reference.

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 metabolic syndrome 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 HR=1.39, respectively) than in females (HR=0.97 and HR=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 HR=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 HR=1.36, respectively) and the 20-39 age group (HR=3.10 and HR=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 HR=1.54, respectively) and the 40-64 age group (HR=1.72 and HR=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

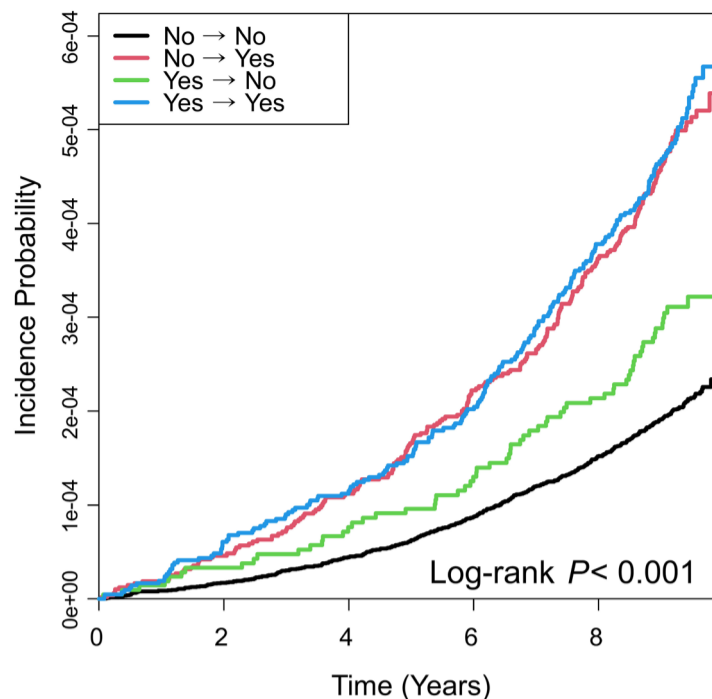


Figure 2. Kaplan-Meier curves showing the cumulative incidence probability of monoclonal gammopathy of undetermined significance by metabolic syndrome status transitions.

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.

Disclosures

No conflicts of interest to disclose.

Contributions

JYL and KH designed the study, 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. 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 Online Supplementary Appendix. Additional data is available from the corresponding author upon reasonable and justified requests.

References

- Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15(12):e538-548.
- Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2006;354(13):1362-1369.
- Kyle RA, Rajkumar SV. Plasma cell disorders. In: Goldman L, Ausiello D, editors. *Cecil Textbook of Medicine.* 22nd ed. Philadelphia: W.B. Saunders; 2004. p. 1184-1195.
- Park HK, Lee KR, Kim YJ, et al. Prevalence of monoclonal gammopathy of undetermined significance in an elderly urban Korean population. *Am J Hematol.* 2011;86(9):752-755.
- Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2018;378(3):241-249.
- Kaur J, Valisekka SS, Hameed M, et al. Monoclonal gammopathy of undetermined significance: a comprehensive review. *Clin Lymphoma Myeloma Leuk.* 2023;23(5):e195-e212.
- Marinac CR, Birmann BM, Lee IM, et al. Body mass index throughout adulthood, physical activity, and risk of multiple myeloma: a prospective analysis in three large cohorts. *Br J Cancer.* 2018;118(7):1013-1019.
- Joseph JM, Hillengass J, Tang L, et al. Dietary risk factors for monoclonal gammopathy of undetermined significance in a racially diverse population. *Blood Adv.* 2024;8(3):538-548.
- Lee DJ, El-Khoury H, Tramontano AC, et al. Mass spectrometry-detected mgus is associated with obesity and other novel modifiable risk factors in a high-risk population. *Blood Adv.* 2024;8(7):1737-1746.
- Urvi A. Shah LLC, Andriy Derkach, et al." → " Shah UA, Cogrossi LL, Derkach A, et al. A high-fiber dietary intervention (NUTRIVENTION) in precursor plasma cell disorders improves biomarkers of disease and may delay progression to myeloma. *Blood.* 2024;144(Suppl 1):671.
- Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011-2016. *JAMA.* 2020;323(24):2526-2528.
- Park D, Shin MJ, Després JP, et al. 20-year trends in metabolic syndrome among Korean adults from 2001 to 2020. *JACC Asia.* 2023;3(3):491-502.
- Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24(4):683-689.
- Esposito K, Chiodini P, Colao A, et al. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care.* 2012;35(11):2402-2411.
- Parida S, Siddharth S, Sharma D. Adiponectin, obesity, and cancer: clash of the bigwigs in health and disease. *Int J Mol Sci.* 2019;20(10):2519.
- Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the national health information database of the national health insurance service in South Korea. *Int J Epidemiol.* 2017;46(3):799-800.
- Kim DS. Introduction: health of the health care system in Korea. *Soc Work Public Health.* 2010;25(2):127-141.
- Third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii) final report. *Circulation.* 2002;106(25):3143-3421.
- Kim JA, Yoon S, Kim LY, et al. Towards actualizing the value potential of Korea health insurance review and assessment (hira) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of hira data. *J Korean Med Sci.* 2017;32(5):718-728.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med.* 1965;58(5):295-300.
- Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature.* 2011;473(7347):317-325.
- Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;444(7121):860-867.
- Coussens LM and Werb Z. Inflammation and cancer. *Nature.* 2002;420(6917):860-867.
- Kristinsson SY, Koshiol J, Björkholm M, et al. Immune-related and inflammatory conditions and risk of lymphoplasmacytic lymphoma or Waldenström macroglobulinemia. *J Natl Cancer Inst.* 2010;102(8):557-567.
- Birmann BM, Neuhaus ML, Rosner B, et al. Prediagnosis biomarkers of insulin-like growth factor-1, insulin, and interleukin-6 dysregulation and multiple myeloma risk in the multiple myeloma cohort consortium. *Blood.* 2012;120(25):4929-4937.
- Donath MY and Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol.* 2011;11(2):98-107.
- Chang SH, Luo S, Thomas TS, et al. Obesity and the transformation of monoclonal gammopathy of undetermined significance to multiple myeloma: a population-based cohort study. *J Natl Cancer Inst.* 2017;109(5):djw264.
- Karastergiou K, Smith SR, Greenberg AS, et al. Sex differences in human adipose tissues - the biology of pear shape. *Biol Sex Differ.* 2012;3(1):13.
- Sigurbergsson A, Rögnvaldsson S, Thorsteinsdóttir S, et al. Disease associations with monoclonal gammopathy of undetermined significance can only be evaluated using screened cohorts: results from the population-based iStopMM study. *Haematologica.* 2023;108(12):3392-3398.