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Associations between Neutrophil-to-lymphocyte Ratio and Autoimmune Diseases:

Evidence from a Large Prospective Cohort Study

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BACKGROUND

- Autoimmune diseases are characterized by inflammation and immune dysregulation
- Neutrophils and lymphocytes play crucial roles in immune system regulation and may be associated with the development and progression of autoimmune diseases
- While the neutrophil-to-lymphocyte ratio (NLR) is an important emerging indicator of inflammation, evidence is limited by cross-sectional associations and sample sizes

AIMS

- Aim 1:** To investigate the association between NLR and incidence of any autoimmune disease in a prospective cohort
- Aim 2:** To explore the association between NLR and individual autoimmune diseases

METHODS

Study Population

- Prospective cohort study among participants who completed blood count measures in the UK Biobank from 2006 to 2010 (N = 430,347)

Blood Counts Measurement

- White blood cell (WBC) and their subtypes (lymphocytes, neutrophils, monocytes, eosinophils, basophils) measured at baseline

- NLR was categorized into quartiles

Outcome Ascertainment

- 40 types of autoimmune diseases defined using ICD-9/10 codes

Statistical Analysis

- A lag-time of 2-year was adopted to minimize reverse causality
- Hazard ratios (HR) and 95% confidence intervals (CI) by multivariable Cox regression for per quartile NLR increase
- Potential confounders of sociodemographic (age, sex, race, income, education), lifestyle factors (BMI, alcohol, smoking behavior), comorbidities, and WBC were adjusted in the Cox regression model
- Bonferroni correction was used to account for multiple comparison
- Spline curve was fitted to identify nonlinear effects
- Subgroup analysis: p-for-interaction was calculated to identify heterogeneity for subgroups (age, sex)
- Sensitivity analysis: varying lag time of 5-year and excluding immunocompromised patients

RESULTS

Table 1. Baseline characteristics of the study population for overall and quartiles of NLR in UK biobank

	Q1 (N=107,656)	Q2 (N=107,518)	Q3 (N=107,589)	Q4 (N=107,584)
Demographic, 2006-2010				
Age, mean (SD)	56.24 (7.82)	56.34 (8.02)	56.33 (8.17)	56.66 (8.37)
Female sex	64,109 (59.5)	60,652 (56.4)	57,126 (53.1)	50,216 (46.7)
Race/Ethnicity				
White	96,759 (89.9)	101,866 (94.7)	103,110 (95.8)	103,971 (96.6)
Asian	3,619 (3.4)	2,519 (2.3)	2,019 (1.9)	1,512 (1.4)
Black	4,377 (4.1)	1,149 (1.1)	689 (0.6)	478 (0.4)
Mixed	720 (0.7)	655 (0.6)	593 (0.6)	557 (0.5)
Other	2,181 (2.0)	1,329 (1.2)	1,178 (1.1)	1,066 (1.0)
Socioeconomic				
TDI	-1.29 (3.12)	-1.43 (3.02)	-1.40 (3.04)	-1.27 (3.10)
Education				
Low	34,775 (32.3)	35,380 (32.9)	36,323 (33.8)	38,211 (35.5)
Medium	34,278 (31.8)	34,910 (32.5)	35,342 (32.8)	34,889 (32.4)
High	37,248 (34.6)	35,992 (33.5)	34,757 (32.3)	33,284 (30.9)
Unknown	1,355 (1.3)	1,236 (1.1)	1,167 (1.1)	1,200 (1.1)
Health Behaviors				
Smoking behavior				
Never	59,991 (55.7)	59,120 (55.0)	59,183 (55.0)	58,507 (54.4)
Previous	36,827 (34.2)	37,131 (34.5)	36,796 (34.2)	36,293 (33.7)
Current	10,286 (9.6)	10,778 (10.0)	11,105 (10.3)	12,252 (11.4)
Unknown	552 (0.5)	489 (0.5)	505 (0.5)	532 (0.5)
Alcohol consumption				
Never	5,361 (5.0)	4,438 (4.1)	4,305 (4.0)	4,123 (3.8)
Previous	3,514 (3.3)	3,427 (3.2)	3,496 (3.2)	3,859 (3.6)
Current	98,484 (91.5)	99,431 (92.5)	99,571 (92.5)	99,344 (92.3)
Unknown	297 (0.3)	222 (0.2)	217 (0.2)	258 (0.2)
BMI, kg/m ²				
Underweight (<18.5)	402 (0.4)	438 (0.4)	493 (0.5)	622 (0.6)
Normal (18.5-24.9)	34,510 (32.1)	33,916 (31.5)	34,114 (31.7)	36,322 (33.8)
Overweight (25.0-29.9)	46,883 (43.5)	46,690 (43.4)	46,415 (43.1)	45,368 (42.2)
Obese (30+)	25,861 (24.0)	26,474 (24.6)	26,567 (24.7)	25,272 (23.5)
Comorbidities				
Cardiovascular diseases	4,256 (4.0)	4,767 (4.4)	5,476 (5.1)	6,968 (6.5)
Hypertension	24,989 (23.2)	26,538 (24.7)	28,313 (26.3)	31,439 (29.2)
Dyslipidemia	14,565 (13.5)	15,066 (14.0)	15,496 (14.4)	16,814 (15.6)
Diabetes	4,467 (4.1)	4,394 (4.1)	4,708 (4.4)	5,590 (5.2)
Cancer	9,199 (8.5)	9,137 (8.5)	9,241 (8.6)	10,774 (10.0)
Lab test				
White blood cell count	6.36 (2.60)	6.62 (1.56)	6.91 (1.62)	7.53 (1.93)
Neutrophil count	3.18 (0.92)	3.88 (0.95)	4.39 (1.07)	5.33 (1.52)
Lymphocyte count	2.48 (1.99)	2.06 (0.50)	1.83 (0.45)	1.52 (0.42)
NLR	1.34 (0.25)	1.89 (0.13)	2.40 (0.18)	3.65 (1.53)

Note: Q, quartile; SD, standard deviation; TDI, Townsend deprivation index; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio

Figure 2. Associations between NLR and individual autoimmune diseases

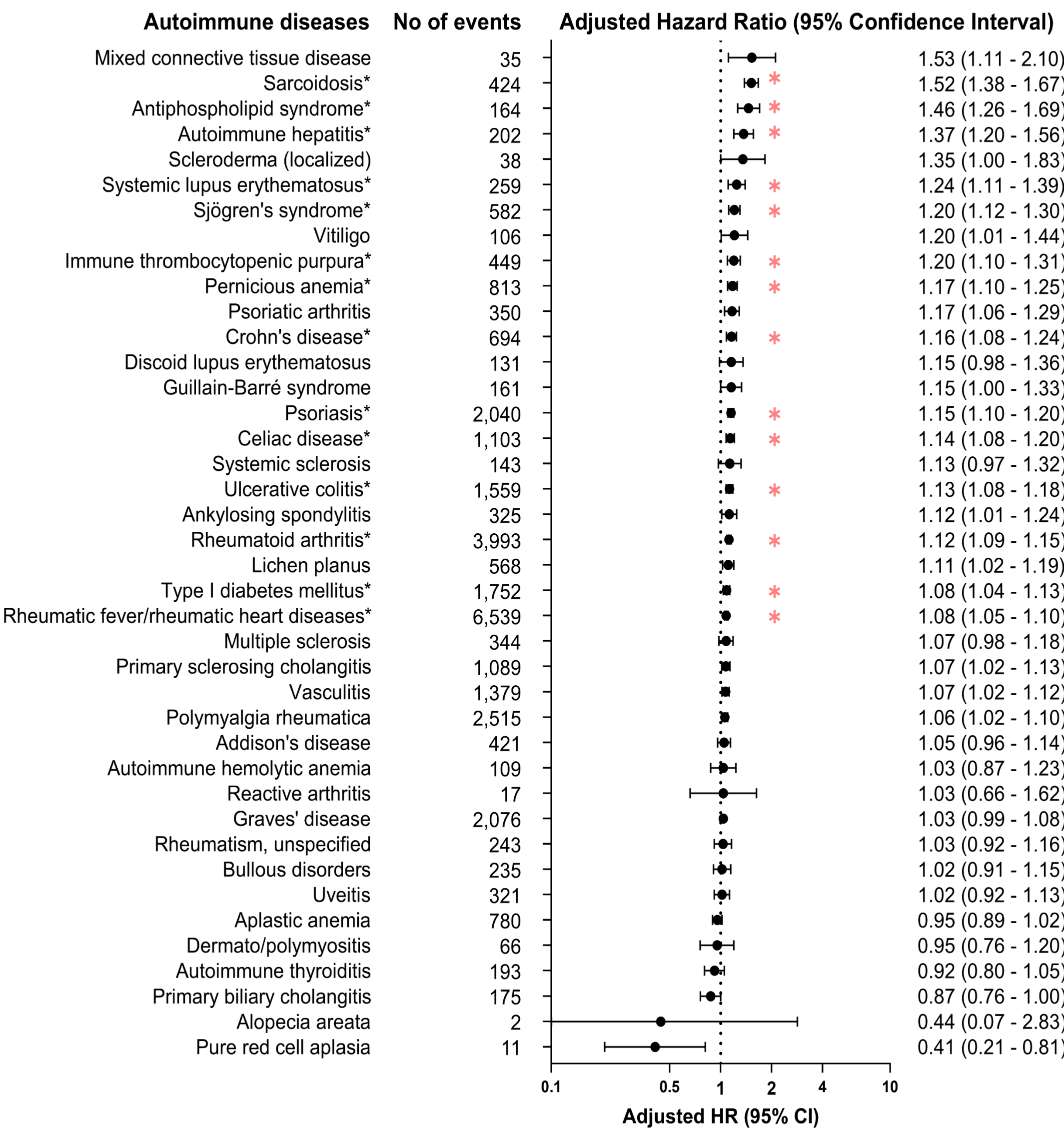


Figure 1. NLR distributions of NLR level by baseline characteristics

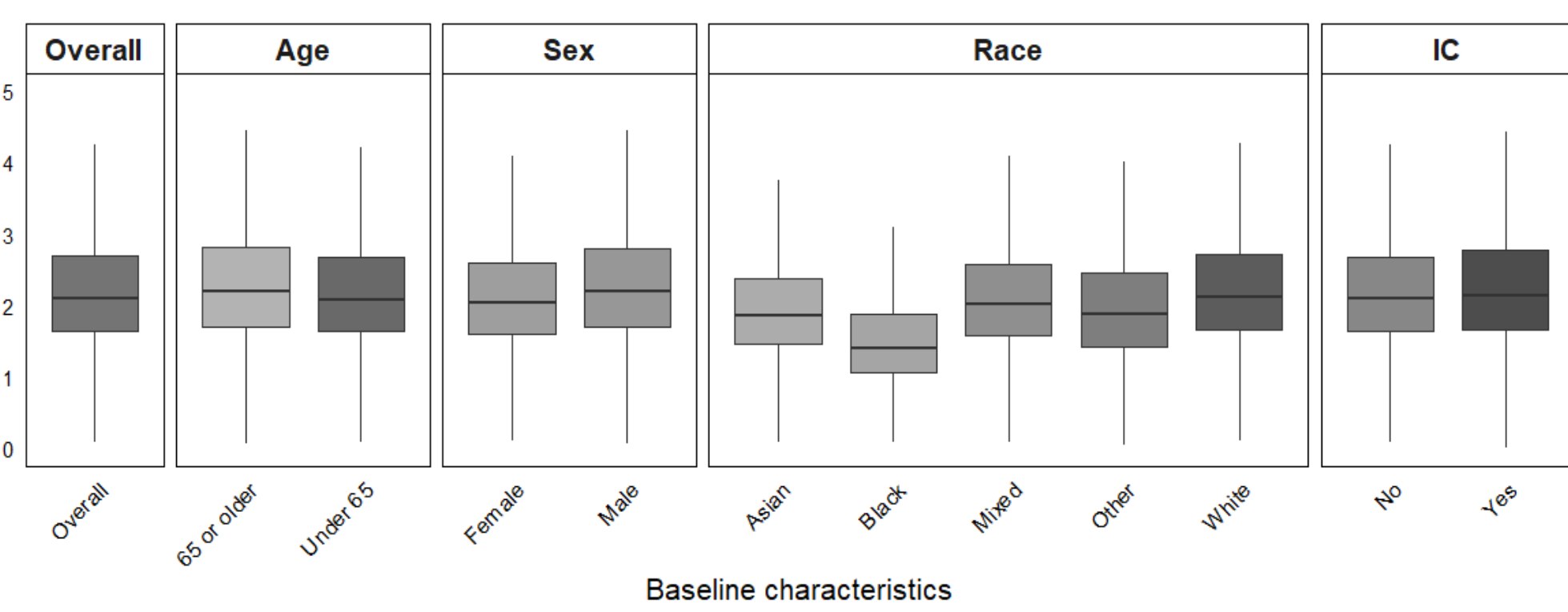


Figure 3. Cumulative incidence curve of any autoimmune disease by quartile increases of NLR

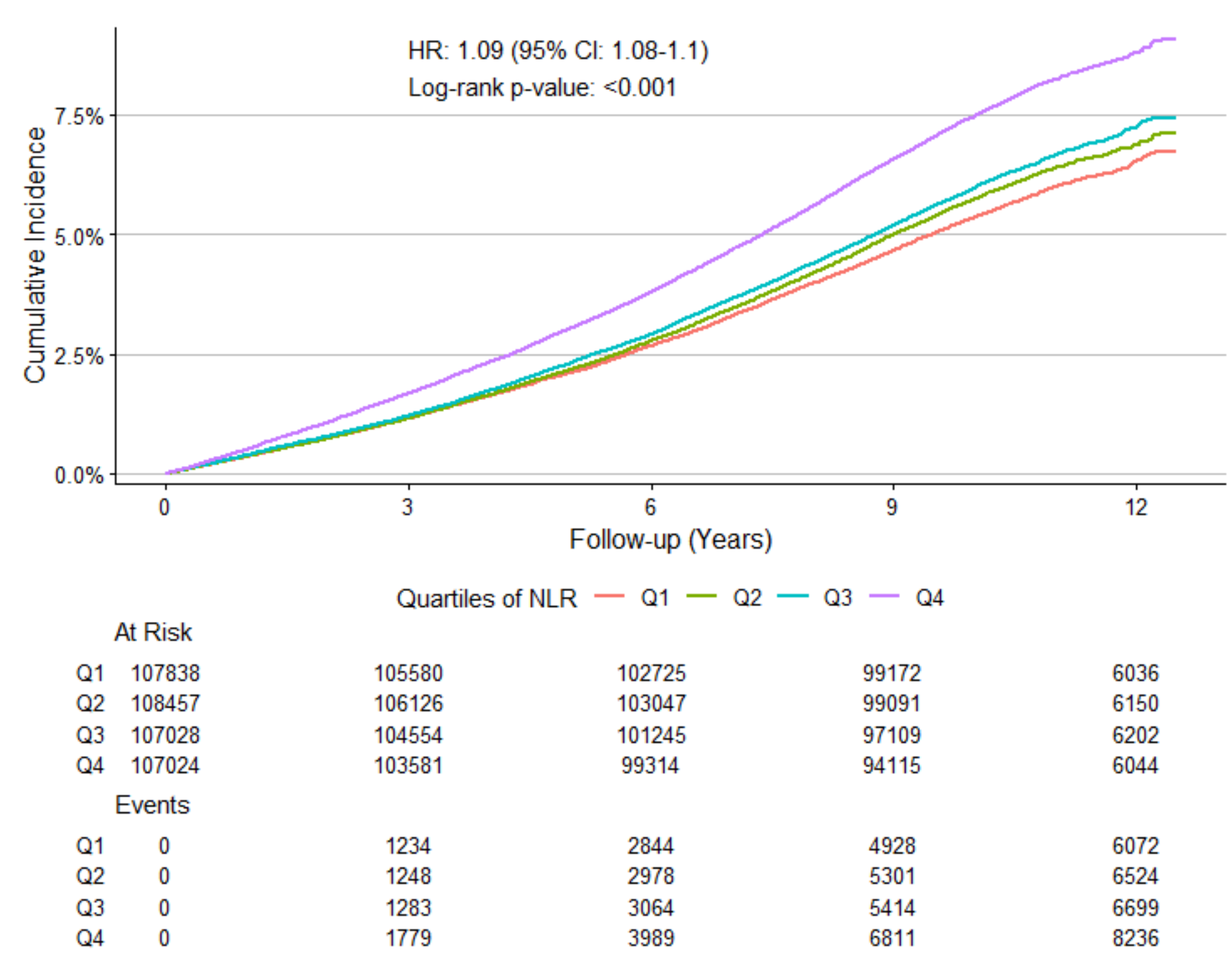


Figure 4. Spline curve of NLR and risk of autoimmune diseases

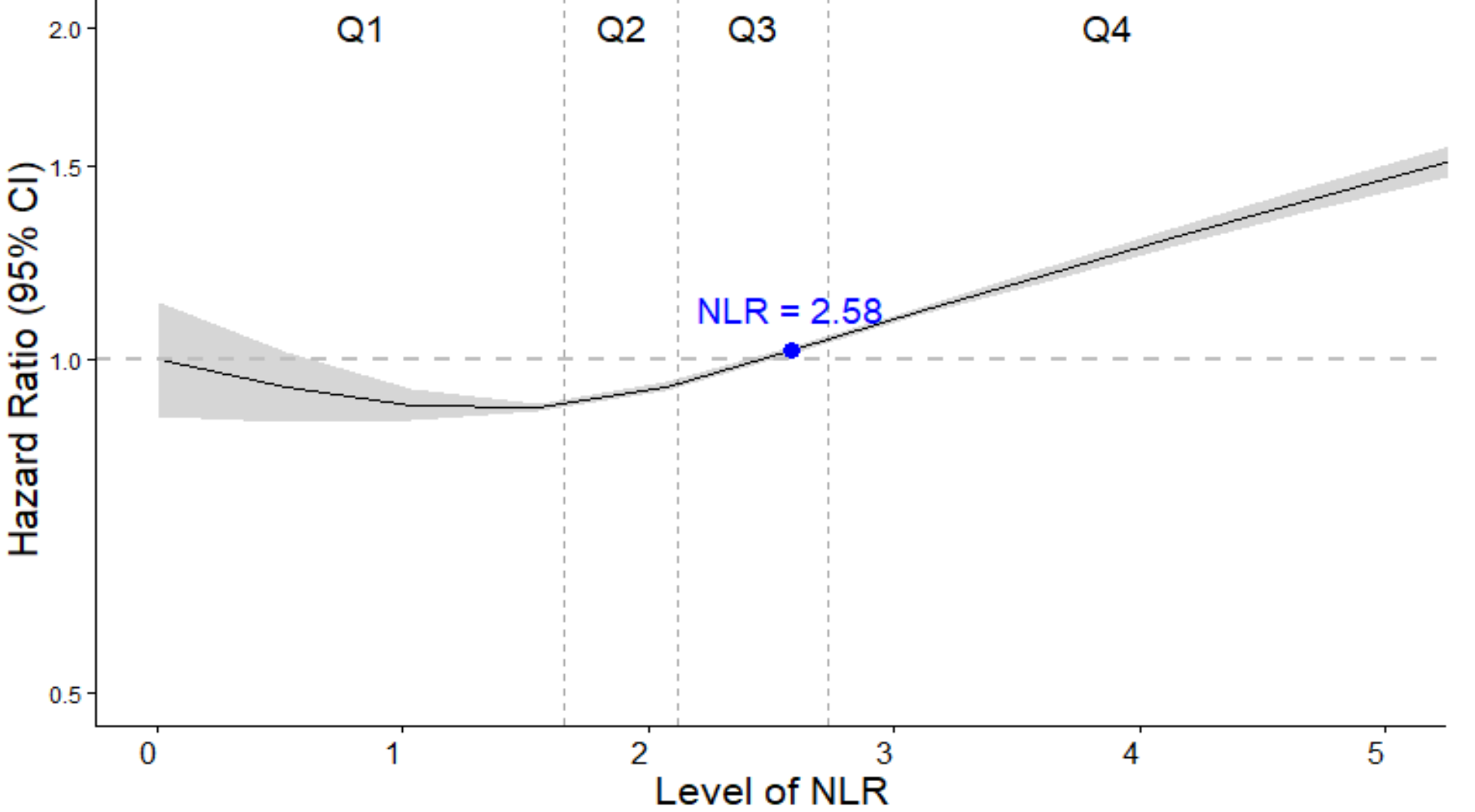


Table 2. Associations between NLR and any autoimmune diseases by subgroup and sensitivity analyses

	Events	Per Q increase HR (95% CI)*	Q4 vs. Q1 HR (95% CI)*
Main analysis			
	27,571	1.09 (1.07-1.10)	1.30 (1.26-1.35)
Subgroup analysis			
Age			
Age ≥ 65	8,724	1.09 (1.07-1.10)	1.31 (1.23-1.39)
Age < 65	18,847	1.09 (1.08-1.11)	1.29 (1.24-1.34)
Sex			
Female	15,062	1.08 (1.07-1.10)	1.28 (1.22-1.34)
Male	12,509	1.09 (1.08-1.11)	1.32 (1.25-1.39)
Sensitivity analysis			
5-year lag time	22,027	1.09 (1.07-1.10)	1.29 (1.24-1.34)
Excluding patients with IC	24,389	1.09 (1.08-1.11)	1.32 (1.27-1.37)

Note: Q, quartile; HR, hazard ratio; CI, confidence interval; IC, immunocompromised
*Adjusted for sociodemographic variables (age, sex, race/ethnicity, income, education, and TDI), health behaviors (smoking, alcohol consumption, and BMI), comorbidities (cardiovascular diseases, hypertension, dyslipidemia, diabetes, and cancer), and white blood cell counts.

CONCLUSIONS

- To our knowledge, this is the first study to examine the links between NLR and a comprehensive list of autoimmune diseases in a large population-based cohort, demonstrating a significant positive association between NLR and autoimmune conditions.
- Neutrophils and lymphocytes may contribute to develop autoimmune diseases by forming neutrophil extracellular traps and regulating immune responses, further clarifying the pathophysiological mechanisms connecting inflammation to autoimmune disease.
- This study suggests the potential of NLR as a pre-clinical marker of inflammation, aiding the early diagnosis and risk assessment for autoimmune diseases.