scientific reports

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Inflammatory markers mediate the association between weight-adjusted waist circumference and mortality in patients with cardiometabolic syndrome

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Cardiometabolic Syndrome (CMS) is associated with increased risks of cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality. The Weight-Adjusted Waist Circumference Index (WWI) has emerged as a novel metric for assessing obesity and its health implications. To investigate the relationship between WWI and mortality in CMS patients, considering the mediating role of inflammatory markers. The study analyzed the National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2018 and identified 6506 patients with CMS. WWI was calculated as the square root of waist circumference (cm) divided by weight (kg). Mortality data were correlated with the National Death Index (NDI). Cox regression models, adjusted for demographic and clinical covariates, assessed the effect of WWI on all-cause and cause-specific mortality. Finally, the role of inflammatory markers in the relationship between WWI and mortality was explored using mediation analysis. The study observed a positive linear association between WWI and all-cause, cardiovascular, and diabetes-related mortalities among CMS patients. After adjusting for demographic and clinical confounders, WWI remained a significant predictor of mortality. Mediation analysis revealed that inflammatory markers, particularly the neutrophil and systemic immune-inflammation index (SII), significantly mediated the relationship between WWI and all-cause mortality. WWI is an independent predictor of mortality in CMS patients, with inflammation potentially linking obesity to mortality risk. These findings may inform clinical risk assessment and management strategies for CMS.

Keywords Cardiometabolic Syndrome, Weight-Adjusted Waist Circumference Index, Mortality, Inflammatory Markers, Mediation Analysis, NHANES

Cardiometabolic Syndrome (CMS) is a cluster of metabolic disorders centered around insulin resistance, encompassing abdominal obesity, hypertension, hyperglycemia, and dyslipidemia[1–3]. This syndrome significantly elevates the risk of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and all-cause mortality[4]. According to the World Health Organization (WHO), CMS is one of the leading contributors to global mortality and disability, with an increasing prevalence over the past few decades[5]. Reports from the Centers for Disease Control and Prevention (CDC) indicate that the risk of metabolic syndrome across the United States is approximately one in three[5]. In recent years, factors such as unhealthy diet, physical inactivity, obesity, and an aging population have further accelerated the epidemic of CMS[6–9]. Despite a plethora of research examining factors associated with the increased or decreased incidence of cardiometabolic syndrome, understanding of the long-term trends and determinants of all-cause mortality among patients with CMS remains limited.

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Chronic inflammation is recognized as a key factor in the onset and progression of CVD and T2DM and is strongly associated with poor prognosis[10]. The presence and severity of systemic inflammation can be predicted using a variety of inflammatory markers that reflect the presence and severity of inflammation throughout the body and the poor outcome of these diseases. The systemic immune-inflammation index (SII) has been shown to have a substantial predictive value for poor prognosis in myocardial infarction patients with diabetes mellitus[11]. Elevated systemic inflammation response index (SIRI) has also been shown to be strongly associated with the risk of death in obese populations[12]. At the same time, previous studies have shown that chronic low-grade inflammation can mediate the adverse outcomes associated with excessive obesity[13]. Thus, systemic inflammation may have a potential role in mediating obesity-related long-term prognosis.

Traditionally, body mass index (BMI) and waist circumference (WC) have been employed as metrics to assess obesity and its associated health risks. However, the limitations of these indices in accurately reflecting the distribution of individual fat and lean mass have become increasingly recognized[14,15]. For instance, BMI does not differentiate between the proportion of fat and muscle in body weight, while WC, although indicative of abdominal fat, overlooks other critical factors such as height[16,17]. In recent years, the Weight-Adjusted Waist Circumference Index (WWI) has emerged as a novel obesity assessment tool. By considering the ratio of an individual's weight to WC, WWI offers a more precise method of evaluation[18]. The advantage of WWI lies in its ability to provide a more comprehensive assessment of an individual's fat and lean mass, surpassing the limitations of BMI and WC. Consequently, it has demonstrated potential predictive value in various disease domains, including adolescent bone density, female infertility, and erectile dysfunction[19–21]. While previous studies have indicated an association between WWI and various adverse health outcomes, the direct link between WWI and the mortality of CMS patients remains insufficiently investigated.

Therefore, this study is designed to explore the correlation between WWI and the all-cause mortality rate among patients with CMS and further examine the potential mediating role of indicators of inflammation in these relationships. We aim to equip clinicians with more precise tools for risk assessment, thereby enabling the development of more effective preventive and management strategies for individuals with CMS.

Methods

Our study utilized data from the National Health and Nutrition Examination Survey (NHANES), a series of investigations conducted by the CDC in the United States. This survey is designed to assess the health and nutritional status of the civilian, non-institutionalized population in the United States. The NHANES data encompass interview and physical examination results, including demographic, socioeconomic, dietary, and health-related issues, as well as physiological measurements and laboratory tests.

In this survey, we obtained data from the surveys conducted between 2003 and 2018, which included 80,312 participants. Our research focused on adults aged 18 and above, narrowing down the scope to 7,865 respondents with complete CMS data. After excluding those missing WC and weight data (n = 150), incomplete blood cell counts necessary (n = 45), and lacking covariate data (n = 1,164), 6,506 patients were included in the study. The specific screening process is depicted in Fig. 1.

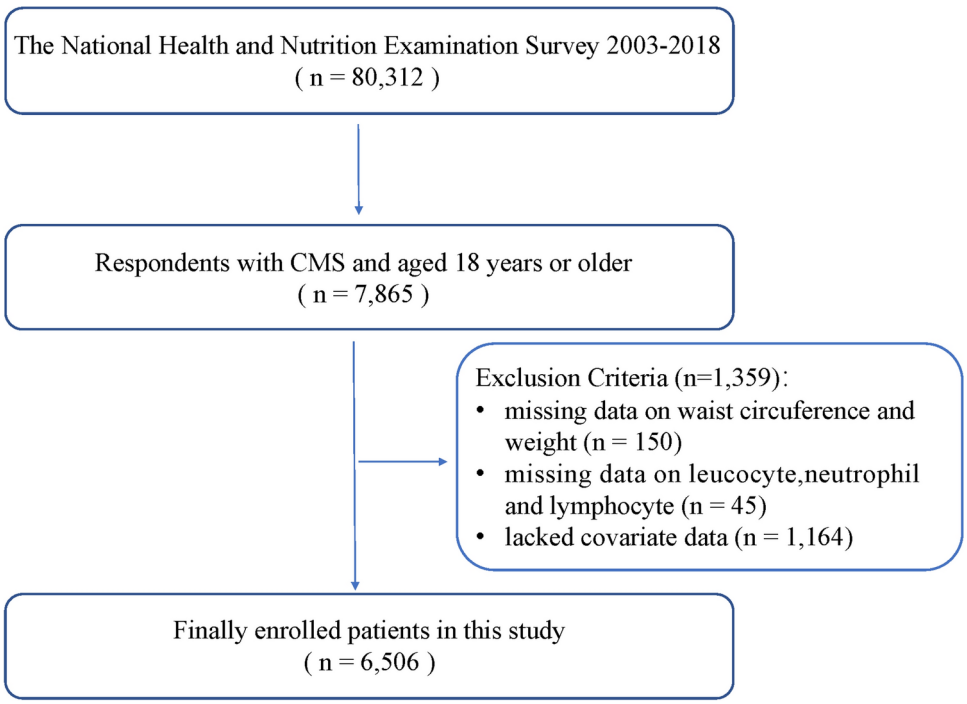

Fig. 1. Study flowchart. CMS, cardiometabolic syndrome.

CMS, WWI, and the definition of death

According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATPIII), the diagnosis of CMS can be made if three or more of the following criteria are present[22]: (1) Abdominal obesity: WC ≥ 102 cm in men, ≥ 88 cm in women; (2) Hypertension: ≥ 130/85 mmHg or on anti-hypertensive medication; (3) Fasting glucose ≥ 100 mg/dL or on diabetes treatment; (4) high-density lipoprotein (HDL): < 40 mg/dL in men, < 50 mg/dL in women; (5) Triglyceride (TG): ≥ 150 mg/dL. WWI is calculated by dividing WC (cm) by the square root of body weight (kg)[23].

In the NHANES database, mortality data are typically obtained by linking records with the National Death Index (NDI). In the NHANES surveys, death is defined as the period from the baseline interview until December 31, 2019. In the analysis, we examined all-cause mortality, cardiovascular mortality, and diabetes-related mortality.

Mediator variable

After sample collection, anticoagulant treatment is administered to prevent blood coagulation. Advanced instruments such as the Beckman Coulter MAXM or HMX are utilized to automatically measure leucocytes, lymphocytes, neutrophils, platelets, and more based on the principles of optics and impedance. The neutrophil-to-lymphocyte ratio (NLR) is calculated by determining the ratio of neutrophils to lymphocytes. The SII is defined as the product of the platelet and the neutrophil divided by the lymphocyte[24].

Selection of covariates

In this study, we selected a set of covariates based on the evidence from previous research and their potential relevance to the study outcomes to control for potential confounding factors and ensure the accuracy of the results[25,26]. These specifically include age, gender, race, education level, marital status, income-to-poverty ratio (PIR), BMI, drinking, smoking status, and medical histories, such as hypertension, diabetes, CVD, and history of cancer. Additionally, we incorporated laboratory measurement indicators, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), HDL, serum albumin, serum uric acid, blood glucose, and estimated glomerular filtration rate (eGFR).

Statistical analysis

We initially conducted descriptive statistics for the baseline characteristics of the participants, utilizing independent samples t-tests or analysis of variance (ANOVA) for between-group comparisons of continuous variables and chi-square tests for categorical variables to assess baseline differences among different exposure groups. Subsequently, we employed a cohort study design and evaluated the relationship between WWI and mortality in patients with CMS using Kaplan–Meier curves. To control for potential confounding factors, we applied multivariate Cox regression analysis, establishing three models (Model 1: unadjusted, Model 2: adjusted for age, gender, and race; Model 3: adjusted for age, gender, race, education level, PIR, marital status, alcohol consumption, smoking status, eGFR, and history of cancer). Additionally, restricted cubic splines were utilized to reflect the dose–response association between WWI and mortality.

To explore the mediating role of inflammatory markers, we first employed a multivariate linear regression model to examine the association between WWI and inflammatory markers. Secondly, we used multivariate Cox regression analysis to investigate the relationship between the mediator variable and mortality rates in patients with CMS. Finally, we conducted mediation analysis using the R package "mediation" to assess the direct and indirect effects of WWI on mortality rates. Precisely, we followed the standard approach in the "mediation" package, which uses a two-step procedure for estimating the mediation effects. In the first step, we fitted the mediator model, where inflammatory markers were treated as the mediator, using a regression model that predicts the mediator based on WWI and other covariates. In the second step, we fitted the outcome model, where mortality rates were predicted based on both WWI and the mediator (inflammatory markers), adjusting for potential confounders. To quantify the mediation effect, we computed the direct effect (the effect of WWI on mortality that is not mediated by inflammation) and the indirect effect (the portion of the effect of WWI on mortality that is mediated by inflammation). The "mediation" package provides the Average Causal Mediation Effect (ACME), which represents the average indirect effect of WWI on mortality through the mediator. The Average Direct Effect (ADE) represents the direct effect of WWI on mortality that is not mediated by inflammation. We also calculated the proportion of mediation, which is the ratio of the indirect effect (ACME) to the total effect (the sum of the direct and indirect effects). This proportion represents the percentage of the total effect of WWI on mortality that is mediated by inflammatory markers. All effects were estimated using 10,000 bootstrap samples to obtain robust confidence intervals, and the significance of the mediation effects was determined using a 95% bootstrap confidence interval (CI). All analyses were performed using R software (version 4.3.1), and a two-tailed P-value < 0.05 was considered statistically significant.

Results

Basic information of participants

In this study, we categorized participants into four quartile groups (Q1 to Q4) based on WWI to assess its association with various baseline characteristics (Table 1). Our research reflects the health information of 32,217,500 individuals across the United States. We found that as WWI increased, the average age of participants, the proportion of females, and the prevalence of hypertension, diabetes, and CVD also increased. Education level and PIR decreased with higher WWI. Additionally, there were significant differences in drinking and smoking habits across different WWI groups, with current drinkers and smokers being more common in the lower

Characteristic	Overall N = 6,506	Q1 N = 1,627	Q2 N = 1,626	Q3 N = 1,626	Q4 N = 1,627	*p*-value
Age, years	53.66 ± 15.41	47.03 ± 13.88	52.49 ± 14.34	56.73 ± 14.92	60.73 ± 15.22	< 0.001
Gender						< 0.001
Male	3,107 (49.98%)	1,002 (64.13%)	884 (56.35%)	764 (47.75%)	457 (25.68%)	
Female	3,399 (50.02%)	625 (35.87%)	742 (43.65%)	862 (52.25%)	1,170 (74.32%)	
Race						0.005
Mexican American	1,171 (8.75%)	216 (7.33%)	320 (9.87%)	302 (9.02%)	333 (9.07%)	
Other Hispanic	629 (4.86%)	118 (3.56%)	173 (6.16%)	168 (5.18%)	170 (4.77%)	
Non-Hispanic white	3,070 (71.56%)	760 (72.07%)	705 (68.95%)	784 (72.03%)	821 (73.40%)	
Non-Hispanic black	1,150 (9.05%)	372 (10.47%)	308 (9.25%)	261 (8.45%)	209 (7.52%)	
Other race	486 (5.78%)	161 (6.57%)	120 (5.77%)	111 (5.32%)	94 (5.24%)	
Education level						< 0.001
Below high school	1,907 (18.77%)	334 (14.25%)	462 (18.24%)	499 (19.84%)	612 (24.39%)	
High school	1,632 (27.21%)	372 (23.74%)	416 (27.08%)	437 (29.71%)	407 (29.39%)	
Above high school	2,967 (54.02%)	921 (62.00%)	748 (54.68%)	690 (50.46%)	608 (46.22%)	
Marital status						< 0.001
Married or living with a partner	3,993 (65.75%)	1,087 (71.40%)	1,065 (68.05%)	1,008 (65.95%)	833 (55.17%)	
Living alone	2,513 (34.25%)	540 (28.60%)	561 (31.95%)	618 (34.05%)	794 (44.83%)	
PIR	2.84 ± 1.59	3.12 ± 1.61	2.91 ± 1.58	2.75 ± 1.60	2.46 ± 1.49	< 0.001
BMI, kg/m^2	33.39 ± 6.85	31.55 ± 5.41	32.58 ± 6.40	34.33 ± 7.01	35.82 ± 7.95	< 0.001
WC, cm	111.61 ± 14.62	104.23 ± 10.48	109.82 ± 12.68	114.91 ± 14.38	120.20 ± 16.19	< 0.001
Alcohol consumption						< 0.001
Never drinkers	996 (12.06%)	169 (8.44%)	219 (11.18%)	242 (11.16%)	366 (18.97%)	
Former drinkers	1,513 (22.64%)	323 (18.20%)	357 (22.48%)	397 (23.58%)	436 (27.85%)	
Current drinkers	3,997 (65.31%)	1,135 (73.37%)	1,050 (66.34%)	987 (65.26%)	825 (53.17%)	
Smoking status						< 0.001
Never smoker	3,273 (49.85%)	864 (56.40%)	800 (48.01%)	768 (43.90%)	841 (49.50%)	
Former smoker	1,959 (31.09%)	397 (25.39%)	509 (32.74%)	544 (34.79%)	509 (32.95%)	
Current smoker	1,274 (19.06%)	366 (18.21%)	317 (19.25%)	314 (21.31%)	277 (17.55%)	
Medical history						
Hypertension	4,475 (65.70%)	952 (55.15%)	1,055 (62.51%)	1,224 (73.35%)	1,244 (75.53%)	< 0.001
Diabetes	2,441 (31.52%)	360 (15.93%)	556 (27.56%)	701 (39.64%)	824 (48.63%)	< 0.001
CVD	1,099 (14.31%)	143 (7.07%)	237 (12.89%)	297 (15.95%)	422 (24.08%)	< 0.001
Cancer	795 (12.76%)	130 (9.41%)	144 (8.96%)	246 (15.24%)	275 (19.08%)	< 0.001
Laboratory measurements						
TC, mmol/L	5.13 ± 1.16	5.20 ± 1.12	5.17 ± 1.16	5.14 ± 1.24	4.99 ± 1.10	< 0.001
TG, mmol/L	2.13 ± 1.53	2.31 ± 1.85	2.11 ± 1.35	2.04 ± 1.51	2.01 ± 1.14	0.019
LDL, mmol/L	3.03 ± 0.98	3.09 ± 0.93	3.07 ± 0.96	3.03 ± 1.06	2.88 ± 0.96	< 0.001
HDL, mmol/L	1.37 ± 0.40	1.38 ± 0.39	1.38 ± 0.41	1.36 ± 0.37	1.39 ± 0.43	0.8
Albumin, g/L	41.73 ± 3.29	42.57 ± 3.19	42.13 ± 3.02	41.44 ± 3.24	40.45 ± 3.34	< 0.001
Uric acid, umol/L	354.02 ± 84.67	358.24 ± 81.05	351.13 ± 83.03	354.72 ± 86.10	350.91 ± 89.54	0.059
Blood glucose, mmol/L	6.78 ± 2.32	6.35 ± 1.97	6.72 ± 2.27	7.02 ± 2.36	7.22 ± 2.67	< 0.001
eGFR, mL/min/1.73m^2	88.73 ± 22.30	93.21 ± 19.11	90.41 ± 20.97	87.55 ± 23.13	81.95 ± 25.06	< 0.001
Leucocyte, 10^9/L	7.58 ± 2.30	7.12 ± 1.99	7.51 ± 2.03	7.77 ± 2.55	8.09 ± 2.55	< 0.001
Lymphocyte, 10^9/L	2.19 ± 1.07	2.15 ± 0.73	2.18 ± 0.71	2.22 ± 1.36	2.21 ± 1.41	0.8
Neutrophil, 10^9/L	4.54 ± 1.69	4.15 ± 1.53	4.48 ± 1.59	4.68 ± 1.75	4.98 ± 1.82	< 0.001
NLR	2.28 ± 1.15	2.07 ± 1.00	2.23 ± 0.97	2.37 ± 1.32	2.53 ± 1.29	< 0.001
SII	564.74 ± 319.16	504.82 ± 264.84	549.56 ± 280.51	584.07 ± 347.92	643.26 ± 374.17	< 0.001
All-cause mortality						< 0.001
Death	5,479 (87.60%)	1,495 (93.91%)	1,419 (89.46%)	1,322 (84.54%)	1,243 (80.12%)	
Alive	1,027 (12.40%)	132 (6.09%)	207 (10.54%)	304 (15.46%)	384 (19.88%)	
Cardiovascular mortality						< 0.001

Continued

Characteristic	Overall N = 6,506	Q1 N = 1,627	Q2 N = 1,626	Q3 N = 1,626	Q4 N = 1,627	*p*-value
Death	6,214 (96.48%)	1,588 (98.51%)	1,567 (96.91%)	1,544 (95.65%)	1,515 (94.07%)	
Alive	292 (3.52%)	39 (1.49%)	59 (3.09%)	82 (4.35%)	112 (5.93%)	
Diabetes mortality						< 0.001
Death	6,340 (98.03%)	1,608 (99.20%)	1,590 (98.47%)	1,580 (97.67%)	1,562 (96.32%)	
Alive	166 (1.97%)	19 (0.80%)	36 (1.53%)	46 (2.33%)	65 (3.68%)	

Table 1. Baseline characteristics according to WWI quartiles. *WWI* Weight-adjusted Waist circumference Index, *PIR* Poverty Income Ratio, *BMI* Body Mass Index, *WC* Waist Circumference, *CVD* Cardiovascular Disease, TC Total Cholesterol, *TG* Triglycerides, *LDL* Low-Density Lipoprotein, HDL High-Density Lipoprotein, *eGFR* estimated Glomerular Filtration Rate, *NLR* Neutrophil-to-Lymphocyte Ratio, *SII* Systemic Immune-inflammation Index.

WWI groups. Indicators such as lipid levels (TC, TG, LDL), leucocyte, NLR, SII, and eGFR showed significant differences across WWI groups, often exhibiting unfavorable health indicators in the higher WWI groups.

Table 2 displays the differences in demographic and clinical characteristics between the survival and death groups. Among the 6,506 participants, significant differences were observed between the two groups in terms of age, race, education level, marital status, PIR, BMI, drinking habits, smoking status, medical history, and laboratory measurement indicators ($P < 0.001$). Notably, the deceased group had a higher average age and a higher prevalence of hypertension, diabetes, and CVD. Furthermore, the deceased group had lower BMI, LDL, uric acid levels, and leucocyte, while higher NLR was observed.

Association between WWI and mortality in CMS patients

During a mean follow-up of 90.8 months, a total of 1027 all-cause deaths, 292 cardiovascular deaths, and 166 diabetes deaths were recorded. In the Kaplan–Meier survival curve analysis, the quartiles of WWI were significantly associated with all-cause mortality, cardiovascular mortality, and diabetes mortality ($P < 0.001$). The risk of death increased progressively with higher WWI. Details of the Kaplan–Meier survival analyses are shown in Fig. 2.

In addition, the Cox proportional hazards model was used to analyze the relationship between WWI and all-cause mortality, diabetes mortality, and cardiovascular mortality in Table 3. In Model 1, which was unadjusted for any covariates, WWI was significantly associated with all three mortality rates, and the hazard ratio (HR) increased with higher WWI. In Model 2, which further adjusted for age, gender, and race, the association between WWI and mortality remained significant, but the HR was somewhat reduced. In Model 3, which fully adjusted for age, gender, race, education level, PIR, marital status, alcohol consumption, smoking status, eGFR, and history of cancer, the positive relationship between WWI and all-cause [HR = 1.53, 95% CI = 1.19–1.98] cardiovascular mortality [HR = 1.84, 95% CI = 1.05–1.3.22] and diabetes mortality [HR = 3.20, 95% CI = 1.56–6.60] still existed. These results indicate that WWI is an independent predictor of mortality, and its impact is independent of multiple potential confounding factors. The P-values for trend tests were all less than 0.05, further confirming the presence of a dose–response relationship between WWI and mortality.

Relationships between WWI and mortality

To ascertain whether there is a nonlinear relationship between WWI and mortality, we employed restricted cubic spline models for further exploration. In the study of WWI in relation to all-cause mortality, it was observed that as WWI increased, the mortality rate among CMS patients gradually rose, and this association was found to be linear (P-non-linear > 0.05; Fig. 3). Similarly, in the investigation of WWI in association with cardiovascular and diabetes mortality risks, RCS analysis confirmed that the positive correlation was linear.

Association between WWI and inflammation

To investigate the effect of inflammation, the correlations of five blood biomarkers of inflammation were analyzed. As shown in Fig. 4, the strongest correlation was found between NLR and SII (r-value = 0.84). There was also a strong correlation between leucocytes and neutrophils (r-value = 0.82). Table 4 shows the relationship between various inflammatory markers and WWI. In the fully adjusted regression model, the results showed a positive correlation with WWI for all markers (all $p < 0.05$).

Association between inflammation and mortality

Cox regression models of inflammatory markers with all-cause mortality and cardiovascular mortality are shown in Table 5. The results showed that leucocyte, neutrophil, NLR and SII were significantly and positively associated with all three mortality outcomes. These associations persisted after adjustment for age, gender, race, and other potential confounders. The association between lymphocytes and all-cause, cardiovascular, and diabetes mortality was not significant in the fully adjusted model.

Intermediary analysis

Finally, mediation analysis was employed to investigate the role of inflammatory markers as mediators in the relationship between WWI and all-cause mortality (Fig. 5). The findings revealed that all four inflammatory

Characteristic	Overall N = 6,506	Alive N = 5,479	Death N = 1,027	p-value
Age, years	53.66 ± 15.41	51.68 ± 14.79	67.59 ± 12.21	< 0.001
Gender				> 0.9
Male	3,107 (49.98%)	2,574 (49.96%)	533 (50.18%)	
Female	3,399 (50.02%)	2,905 (50.04%)	494 (49.82%)	
Race				< 0.001
Mexican American	1,171 (8.75%)	1,046 (9.39%)	125 (4.19%)	
Other Hispanic	629 (4.86%)	569 (5.18%)	60 (2.64%)	
Non-Hispanic white	3,070 (71.56%)	2,412 (70.19%)	658 (81.20%)	
Non-Hispanic black	1,150 (9.05%)	999 (9.16%)	151 (8.22%)	
Other race	486 (5.78%)	453 (6.07%)	33 (3.75%)	
Education level				< 0.001
Below high school	1,907 (18.77%)	1,517 (17.21%)	390 (29.79%)	
High school	1,632 (27.21%)	1,343 (26.80%)	289 (30.07%)	
Above high school	2,967 (54.02%)	2,619 (55.99%)	348 (40.14%)	
Marital status				< 0.001
Married or living with a partner	3,993 (65.75%)	3,459 (66.92%)	534 (57.49%)	
Living alone	2,513 (34.25%)	2,020 (33.08%)	493 (42.51%)	
PIR	2.84 ± 1.59	2.89 ± 1.61	2.46 ± 1.42	< 0.001
BMI, kg/m^2	33.39 ± 6.85	33.62 ± 6.93	31.72 ± 5.99	< 0.001
WC, cm	111.61 ± 14.62	111.76 ± 14.69	110.52 ± 14.09	< 0.001
Alcohol consumption				0.017
Never drinkers	996 (12.06%)	812 (11.45%)	184 (16.35%)	
Former drinkers	1,513 (22.64%)	1,305 (22.81%)	208 (21.44%)	
Current drinkers	3,997 (65.31%)	3,362 (65.74%)	635 (62.21%)	< 0.001
Smoking status				
Never smoker	3,273 (49.85%)	2,873 (51.45%)	400 (38.56%)	
Former smoker	1,959 (31.09%)	1,525 (29.62%)	434 (41.48%)	
Current smoker	1,274 (19.06%)	1,081 (18.93%)	193 (19.96%)	
Medical history				< 0.001
Hypertension	4,475 (65.70%)	3,589 (62.93%)	886 (85.23%)	
Diabetes	2,441 (31.52%)	1,888 (28.82%)	553 (50.58%)	
CVD	1,099 (14.31%)	711 (11.05%)	388 (37.38%)	< 0.001
Cancer	795 (12.76%)	564 (11.20%)	231 (23.72%)	
Laboratory measurements				0.048
TC, mmol/L	5.13 ± 1.16	5.14 ± 1.14	5.06 ± 1.25	0.3
TG, mmol/L	2.13 ± 1.53	2.14 ± 1.56	2.12 ± 1.23	< 0.001
LDL, mmol/L	3.03 ± 0.98	3.05 ± 0.97	2.85 ± 1.05	< 0.001
HDL, mmol/L	1.37 ± 0.40	41.84 ± 3.24	41.00 ± 3.52	0.001
Albumin, g/L	41.73 ± 3.29	352.14 ± 82.79	367.29 ± 95.92	< 0.001
Uric acid, umol/L	354.02 ± 84.67	6.69 ± 2.18	7.45 ± 3.07	0.008
Blood glucose, mmol/L	6.78 ± 2.32	1.37 ± 0.40	1.41 ± 0.40	0.095
eGFR, mL/min/1.73m2	88.73 ± 22.30	91.24 ± 20.95	70.99 ± 23.51	< 0.001
Leucocyte, 109/L	7.58 ± 2.30	7.54 ± 2.14	7.89 ± 3.19	< 0.001
Lymphocyte, 109/L	2.19 ± 1.07	2.20 ± 0.84	2.13 ± 2.06	< 0.001
Neutrophil, 109/L	4.54 ± 1.69	4.50 ± 1.65	4.82 ± 1.91	< 0.001
NLR	2.28 ± 1.15	2.21 ± 1.02	2.75 ± 1.76	< 0.001
SII	564.74 ± 319.16	551.88 ± 290.33	655.55 ± 465.55	0.2
WWI	11.57 ± 0.69	11.44 ± 0.69	11.80 ± 0.68	< 0.001

Table 2. Baseline characteristics between the survival and death groups. *WWI* Weight-adjusted Waist circumference Index, *PIR* Poverty Income Ratio, *BMI* Body Mass Index, *WC* Waist Circumference, *CVD* Cardiovascular Disease, *TC* Total Cholesterol, *TG* Triglycerides, *LDL* Low-Density Lipoprotein, *HDL* High-Density Lipoprotein, *eGFR* Estimated Glomerular Filtration Rate, *NLR* Neutrophil-To-Lymphocyte Ratio, *SII* Systemic Immune-Inflammation Index.

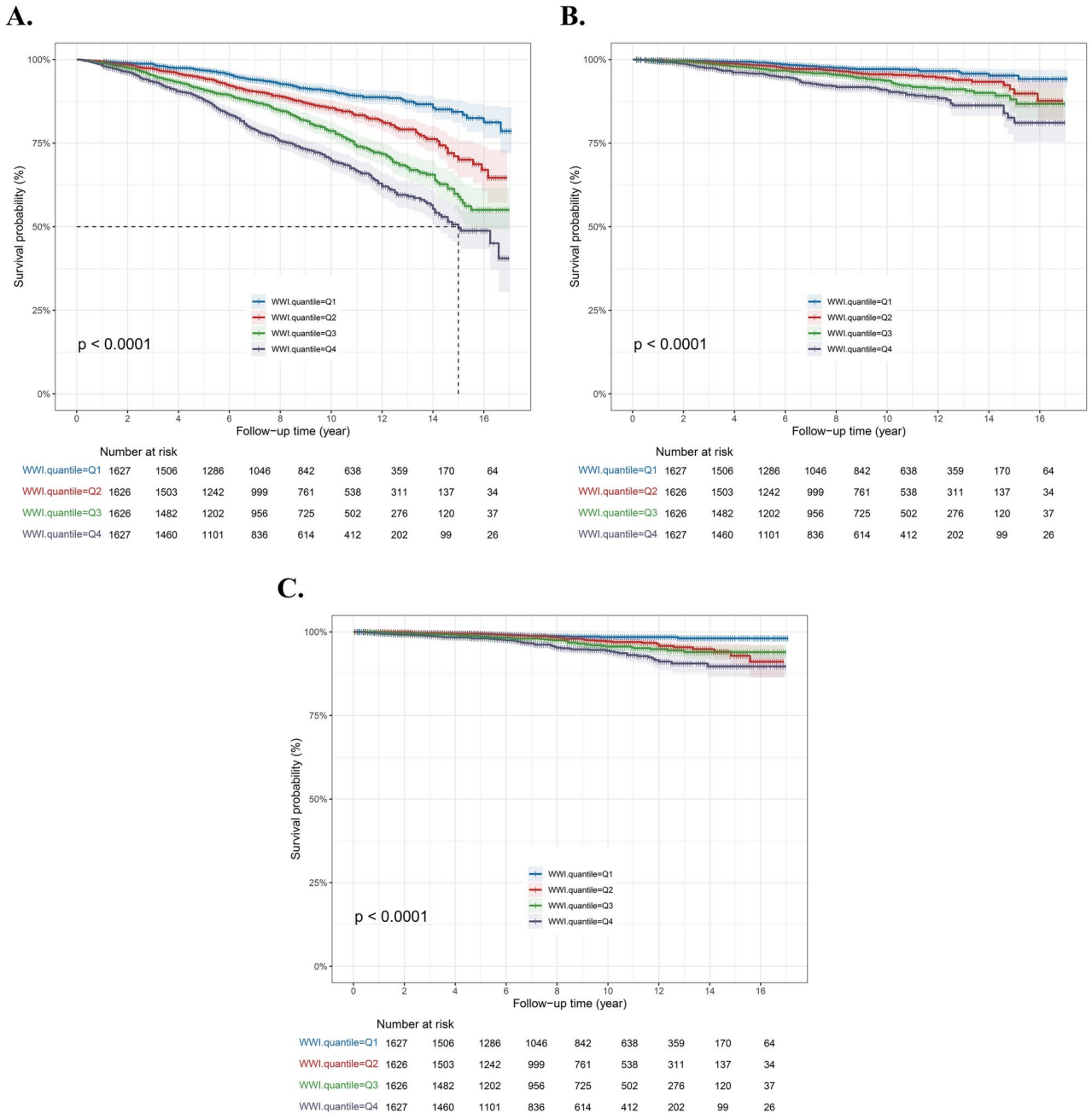

Fig. 2. Kaplan–Meier analyses for all-cause mortality (**A**), cardiovascular mortality (**B**) and diabetes mortality (**C**) among the four groups. Q1-Q4 quartiles 1–4; WWI, weight-adjusted waist circumference index.

markers significantly mediated the relationship between WWI and all-cause mortality, with leucocyte, neutrophils, NLR and SII accounting for 14.6%, 24.52%, 17.7% and 22.64% of the total, respectively ($P < 0.05$).

Discussion

This study utilized the NHANES database to investigate the association between WWI and all-cause mortality among patients with CMS and further analyzed the potential mediating role of inflammatory markers in this relationship. The results indicated that WWI was positively correlated with all-cause mortality, cardiovascular mortality, and diabetes mortality in CMS patients, and these associations remain highly uniform across the different adjustment models. These results strongly indicate that WWI is an independent predictor of mortality, and its predictive value remains significant even after adjusting for a wide range of demographic, clinical, and behavioral factors. Additionally, inflammatory markers, particularly leucocytes, neutrophils, NLR and SII, were found to mediate the relationship between WWI and all-cause mortality. These findings highlight the potential mediating role of inflammatory markers in the link between obesity and mortality risk, underscoring the significance of obesity-related inflammation in all-cause mortality.

Exposure	Model 1 HR (95% CI) *p*-value	Model 2 HR (95% CI) *p*-value	Model 3 HR (95% CI) *p*-value
All-cause mortality			
WWI (continuous)	**2.19 (1.99, 2.41) <0.001**	**1.44 (1.27, 1.63) <0.001**	**1.31(1.14, 1.50) <0.001**
WWI quartile			
Quartile 1	Reference	Reference	Reference
Quartile 2	**1.95 (1.49, 2.54) <0.001**	1.29 (0.90, 1.68) 0.059	1.16 (0.89, 1.51) 0.261
Quartile 3	**2.95 (2.35, 3.71) <0.001**	**1.54 (1.22, 1.93) <0.001**	**1.33 (1.06, 1.67) 0.013**
Quartile 4	**4.54 (3.62, 5.69) <0.001**	**1.90 (1.48, 2.44) <0.001**	**1.53 (1.19, 1.98) 0.001**
P for trend	**<0.001**	**<0.001**	**<0.001**
Diabetes mortality			
WWI (continuous)	**2.61 (2.14, 3.17) <0.001**	**2.14 (1.64, 2.78) <0.001**	**1.84 (1.40,2.41) <0.001**
WWI quartile			
Quartile 1	Reference	Reference	Reference
Quartile 2	**2.16 (1.09,4.28) 0.027**	1.67 (0.82, 3.41) 0.155	1.49 (0.72, 3.06) 0.278
Quartile 3	**3.41 (1.73, 6.70) <0.001**	**2.33 (1.15, 4.70) 0.018**	2.03 (0.96, 4.31) 0.063
Quartile 4	**6.42 (3.51, 11.7) <0.001**	**3.90 (1.96, 7.76) <0.001**	**3.20 (1.56, 6.60) 0.001**
P for trend	**<0.001**	**<0.001**	**0.001**
Cardiovascular mortality			
WWI (continuous)	**2.41 (2.01, 2.89) <0.001**	**1.61 (1.28, 2.01) <0.001**	**1.45 (1.15, 1.84) 0.002**
WWI quartile			
Quartile 1	Reference	Reference	Reference
Quartile 2	**2.32 (1.30, 4.14) 0.004**	1.53 (0.83, 2.79) 0.169	1.40 (0.75, 2.60) 0.288
Quartile 3	**3.37 (2.22, 5.12) <0.001**	**1.71 (1.10, 2.64) 0.016**	1.56 (1.00, 2.43) 0.052
Quartile 4	**5.46 (3.30, 9.02) <0.001**	**2.24 (1.32, 3.78) 0.002**	**1.84 (1.05, 3.22) 0.032**
P for trend	**<0.001**	**<0.001**	**0.001**

Table 3. Multivariable Cox regression analyses for all-cause and cause-specific mortality in patients with WWI.
Model 1: No covariates were adjusted. Model 2: Age, gender, and race were adjusted. Model 3: Age, gender, race, education level, PIR, marital status, alcohol consumption, smoking status, eGFR, and history of cancer were adjusted. Abbreviation: WWI, weight-adjusted waist circumference index; PIR, the ratio of income to poverty; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

Our findings are consistent with existing literature, which indicates that obesity is a significant risk factor for CVD and T2DM and is associated with an increased risk of all-cause mortality[27,28]. WWI, as an emerging indicator for obesity assessment, provides a more accurate reflection of an individual's fat distribution and body composition compared to traditional BMI and WC, thereby demonstrating greater precision in predicting health risks[23,29]. Previous research has identified the prognostic role of WWI in diseases such as diabetes and asthma[30,31]. A retrospective cohort study from the United States involving 3,223 asthma patients found that for each unit increase in WWI, there is a 43% increase in the risk of all-cause mortality[31]. Furthermore, WWI is associated with a higher risk of death from CVD, cancer, and respiratory issues in patients with asthma. Additionally, a study from China suggested that an increase in WWI negatively affected the daily living activities elderly[32]. In our study, we highlight the potential value of WWI in assessing the mortality risk for CMS patients. Notably, for each unit increase in WWI, the rates of all-cause mortality, cardiovascular mortality, and diabetes mortality increased by 31%, 45%, and 84%, respectively, offering clinicians a more accurate tool for risk assessment.

In addition, our study further explored the correlations between the various inflammatory factors and their mediating role in the relationship between WWI and all-cause mortality. Among them, strong correlations were shown between NLR and SII, as well as leucocytes and neutrophils. This high correlation reflects the overlapping effects of inflammatory responses in patients. NLR is calculated as the ratio of neutrophils to lymphocytes and is widely used as a marker of systemic inflammation. SII combines neutrophil, platelet, and lymphocyte counts to provide a more comprehensive measure of immune activation. The strong correlation between NLR and SII suggests that the two metrics capture similar pathways of inflammation and that neutrophils play a central role in both. The strong correlation between leucocytes and neutrophils suggests that when neutrophil levels increase due to inflammation, the overall leucocyte count also increases, as would be expected in an inflammatory situation. This relationship further emphasizes the key role of neutrophils in systemic inflammation and their potential as a key predictor of poor patient prognosis. Additionally, inflammation is a key component of obesity and CMS, with obesity being considered a state of chronic low-grade inflammation associated with increased white blood cell counts and elevated NLR, both of which are indicators of inflammatory activity[33]. Studies have indicated that leucocytes are linked to an increased risk of metabolic syndrome. For instance, research on non-obese children with leukocytosis and obstructive sleep apnea syndrome has shown correlations between

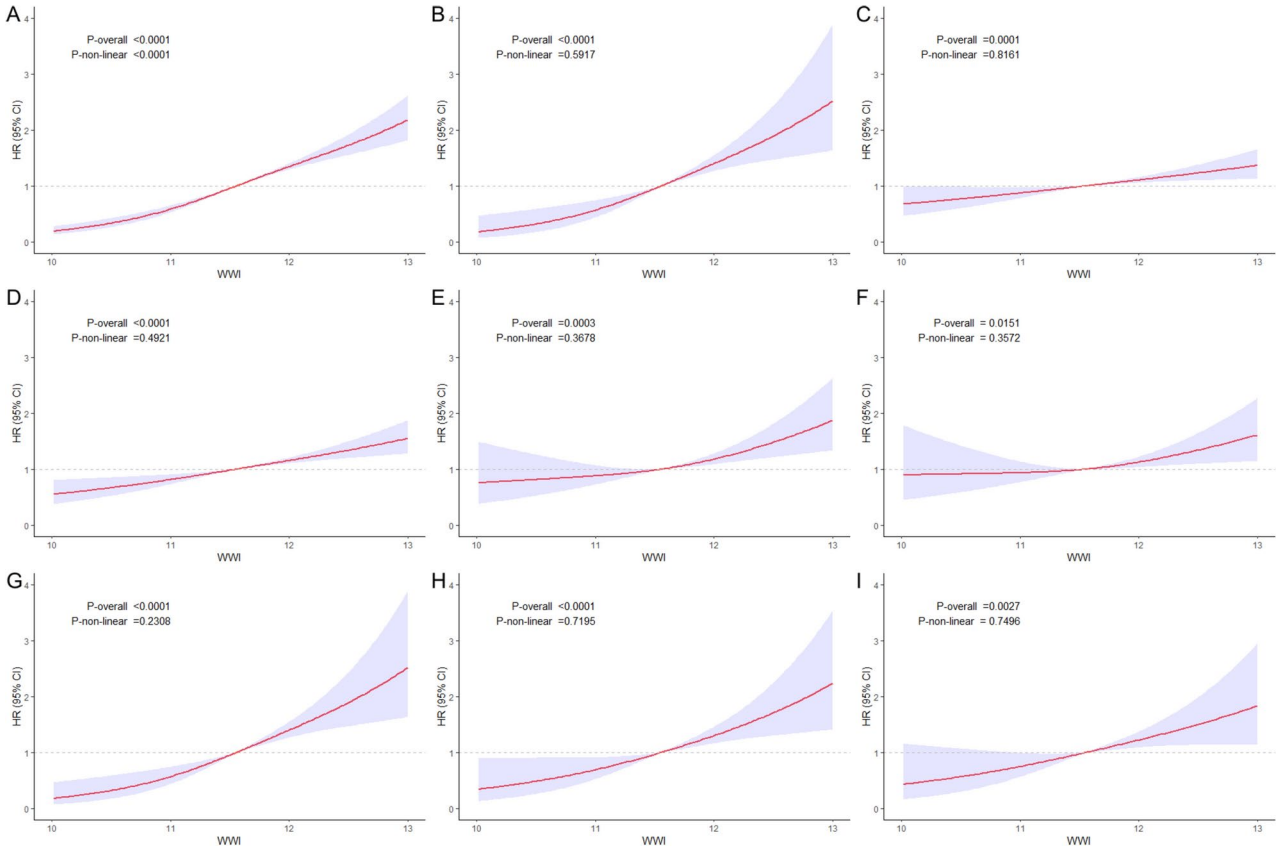

Fig. 3. Association between WWI and all-cause mortality (**A**)(**B**)(**C**), cardiovascular mortality (**D**)(**E**)(**F**), and diabetes mortality (**G**)(**H**)(**I**) in patients with cardiovascular metabolic syndrome. (**A**)(**D**)(**G**) represent unadjusted covariates; (**B**)(**E**)(**H**) are adjusted for age, gender and race; and (**C**)(**F**)(**I**) are adjusted for age, gender, race, education level, PIR, marital status, alcohol consumption, smoking status, eGFR, and history of cancer. The solid line and purple area represent estimates and their corresponding 95% confidence intervals (CIs), respectively. Abbreviation: WWI, weight-adjusted waist circumference index; PIR, the ratio of income to poverty; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

leucocytes and specific components of metabolic syndrome[34,35]. A multicentre study suggests that inflammatory factors mediate the association between obesity index and poor prognosis in hypertensive patients[36]. In our study, inflammatory markers mediated the positive correlation between WWI and mortality rates in CMS patients. The mediating effects were 24.52%, 22.64%, 17.7%, and 14.6% for neutrophils, SII, NLR, and leucocytes respectively. This effect may be facilitated by various mechanisms that promote the development of CVD and diabetes, including atherosclerosis, insulin resistance, and beta-cell dysfunction. As a result, measuring inflammatory markers could help identify CMS patients at higher risk of mortality.

In exploring the underlying mechanisms of these associations, we have identified significant connections between inflammation, obesity, and mortality. Chronic inflammation is thought to be the central bridge between obesity and multiple metabolic and CVD. During obesity, the over-expansion and dysfunction of adipose tissue release various pro-inflammatory factors (e.g., IL-6 and TNF-α), triggering chronic low-grade systemic inflammation[37,38]. This inflammatory state not only extends beyond adipose tissue but also impairs insulin signaling through the activation of inflammatory pathways like nuclear factor-κB (NF-κB). This process induces insulin resistance[39], further disrupting glucose and lipid metabolism and triggering protein kinase C and oxidative stress cascades, which exacerbate atherosclerosis, endothelial dysfunction, and metabolic disorders[39,40]. In addition, elevated free fatty acids and damage-associated molecular patterns (DAMPs) released by adipose tissue apoptosis continue to stimulate the immune system, further exacerbating the spread of chronic inflammation[41,42]. Pro-inflammatory factors trigger vascular injury, fibrosis and microcirculation disorders through abnormal activation of immune cells such as neutrophils and macrophages, thus creating a vicious circle of metabolic disorders and vascular pathology[42]. Meanwhile, oxidative stress increases reactive oxygen species (ROS) levels and depletes nitric oxide (NO), further deteriorating endothelial function[43,44]. Ultimately, chronic inflammation and obesity-associated insulin resistance collaborate to notably elevate the risk of CVD and death in patients with CMS.

Furthermore, chronic inflammation is not only an essential bridge between obesity and cardiovascular metabolic disorders, but is also strongly associated with aging, muscle loss, and the prognosis of chronic diseases. Aging is usually accompanied by a progressive imbalance between the accumulation of stochastic

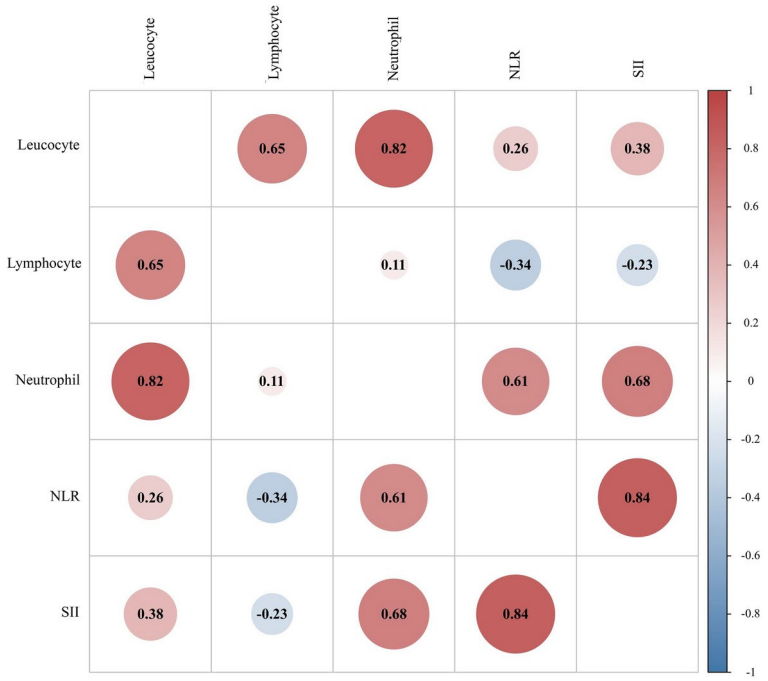

Fig. 4. Correlations of the five blood inflammatory biomarkers. NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

damage and the body's damage repair mechanisms. The chronic mild elevation of inflammatory factors during aging is primarily associated with continued activation of the immune system, as evidenced by elevated levels of circulating inflammatory markers and continued activation of immune cells in circulation and tissues. The chronic inflammatory state resulting from aging has been shown to be strongly associated with an increased risk of death[45]. Higher BMI may provide better nutritional reserve and muscle mass in some cases, especially in patients with chronic diseases or in older age groups. However, weight loss often involves muscle loss, malnutrition, and higher levels of systemic inflammation, all of which can speed up disease progression and impact survival prognosis[46]. Despite the lower BMI and WC in the deceased group, their WWI was significantly higher, suggesting that these individuals may have had more severe visceral adiposity accumulation and muscle loss. In particular, excessive accumulation of visceral adipose tissue induces chronic low-grade inflammation and secretion of inflammatory mediators, which interferes with insulin signaling pathways and leads to insulin resistance[47]. Patients with diabetes mellitus may have increased metabolic disturbances due to long-term insulin resistance and chronic inflammation, which may contribute to the development of atherosclerosis, renal impairment and CVD, all of which are associated with increased all-cause mortality[48]. In addition, hypertension is one of the most important factors affecting survival. Hypertension can lead to vascular damage, atherosclerosis and cardiovascular complications, and inflammation is considered one of the central drivers of elevated blood pressure. Although the inflammatory response is essentially the body's defense mechanism to cope with imbalances in the internal and external environments, when inflammation is unbalanced, it may cause tissue damage and metabolic disorders, thereby increasing the risk of disease progression and death[49].In this study, NLR, serving as a comprehensive indicator of systemic inflammation and immune status, was capable of reflecting the inflammatory load and immunosuppression of the body simultaneously time. The elevated levels of NLR, neutrophils, and leucocytes in the deceased group suggested that the inflammatory response was enhanced and the immune function was impaired. In addition, SII was also elevated in the deceased group. However, it did not reach statistical significance, which may be related to the high heterogeneity of individual inflammation levels or specific disease states.

While our study provides significant insights into the association between WWI and mortality in patients with CMS and reveals the potential role of inflammation, several limitations should be addressed. First, the cross-sectional nature of the NHANES database limits the ability to draw causal inferences since it captures only associations at a single point in time. Second, although we controlled for multiple known confounding factors, such as demographic and clinical variables, there may still be unmeasured confounders, particularly genetic predispositions and lifestyle factors, which could influence the outcomes in ways not fully captured in this study. Genetic factors, such as inherited susceptibility to certain diseases or genetic variations that affect inflammatory responses, could play a significant role in determining an individual's risk for mortality. For example, individuals with genetic variants that predispose them to lower levels of inflammation may have better survival outcomes, regardless of their WWI status. Similarly, lifestyle factors are known to influence both inflammation and mortality outcomes. These factors, if not measured or controlled for, could act as confounders, potentially masking or exaggerating the effect of WWI on mortality. For instance, individuals with healthier lifestyles may exhibit lower levels of inflammation, which could mitigate the adverse impact of WWI on their survival. In contrast,

	β value	95% CI	P value
Leucocyte			
Model 1	0.04	0.03, 0.04	< 0.001
Model 2	0.05	0.04, 0.05	< 0.001
Model 3	0.04	0.04, 0.05	< 0.001
Neutrophil			
Model 1	0.06	0.05, 0.07	< 0.001
Model 2	0.07	0.06, 0.08	< 0.001
Model 3	0.07	0.06, 0.08	< 0.001
Lymphocyte			
Model 1	0.01	−0.01, 0.02	0.44
Model 2	0.02	0.01, 0.03	0.001
Model 3	0.02	0.01, 0.03	0.001
NLR			
Model 1	0.08	0.06, 0.09	< 0.001
Model 2	0.06	0.05, 0.07	< 0.001
Model 3	0.06	0.04, 0.07	< 0.001
SII			
Model 1	0.03	0.02, 0.03	< 0.001
Model 2	0.02	0.02, 0.03	< 0.001
Model 3	0.02	0.02, 0.03	< 0.001

Table 4. The associations between WWI and inflammation-related indicators in patients with cardiometabolic syndrome. Model 1: No covariates were adjusted. Model 2: Age, gender, and race were adjusted. Model 3: Age, gender, race, education level, PIR, marital status, alcohol consumption, smoking status, eGFR, and history of cancer were adjusted. *WWI* Weight-Adjusted Waist Circumference Index, *PIR* The Ratio Of Income To Poverty, *eGFR* Estimated Glomerular Filtration Rate, *NLR* Neutrophil-To-Lymphocyte Ratio, *SII* Systemic Immune-Inflammation Index.

individuals with poor lifestyle choices may have higher inflammatory markers and worse survival, irrespective of their WWI values. These unmeasured factors could lead to residual confounding, potentially biasing our results and limiting the generalizability of our findings. Future research should aim to incorporate genetic data and more comprehensive lifestyle information to better account for these confounders. Additionally, prospective cohort studies, which allow for the establishment of temporal relationships, would provide more substantial evidence for causal inference. Exploring the mediating role of inflammation and examining the impact of genetic and lifestyle factors on the WWI and mortality association would further refine our understanding of these complex interactions.

Conclusion

In summary, the findings of this study highlight the potential value of WWI in assessing the mortality risk among patients with CMS and reveal the mediating role of inflammation between obesity and the risk of mortality. These results provide significant biological insights for the development of preventive and management strategies targeted at CMS patients and may contribute to improving the clinical outcomes for these individuals.

	Model1	Model2	Model3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause mortality			
Leucocyte	1.07 (1.05, 1.09)	1.06 (1.04, 1.09)	1.05 (1.03, 1.08)
Neutrophil	1.13 (1.09, 1.19)	1.22 (1.16, 1.29)	1.17 (1.11, 1.23)
Lymphocyte	0.97 (0.74, 1.28)	1.03 (1.00, 1.07)	1.02 (0.98, 1.06)
NLR	1.21 (1.15, 1.26)	1.15 (1.09, 1.21)	1.15 (1.10, 1.20)
SII	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Diabetes mortality			
Leucocyte	1.10 (1.06, 1.13)	1.09 (1.05, 1.12)	1.08 (1.04, 1.12)
Neutrophil	1.29 (1.16, 1.44)	1.38 (1.24, 1.54)	1.36 (1.21, 1.53)
Lymphocyte	0.83 (0.60, 1.16)	1.00 (0.90, 1.11)	0.99 (0.88, 1.11)
NLR	1.24 (1.17, 1.30)	1.21 (1.16, 1.26)	1.23 (1.17, 1.30)
SII	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Cardiovascular mortality			
Leucocyte	1.06 (1.02, 1.10)	1.06 (1.03, 1.09)	1.04 (1.01, 1.08)
Neutrophil	1.15 (1.08, 1.24)	1.25 (1.16, 1.35)	1.21 (1.12, 1.31)
Lymphocyte	0.66 (0.49, 0.89)	0.95 (0.82, 1.11)	0.91 (0.75, 1.10)
NLR	1.21 (1.14, 1.27)	1.15 (1.07, 1.22)	1.16 (1.10, 1.23)
SII	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

Table 5. The associations of inflammation-related indicators with all-cause mortality and cause-specific mortality. Model 1: No covariates were adjusted. Model 2: Age, gender, and race were adjusted. Model 3: Age, gender, race, education level, PIR, marital status, alcohol consumption, smoking status, eGFR, and history of cancer were adjusted. Abbreviation: PIR, the ratio of income to poverty; eGFR, estimated glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; HR, hazard ratio; CI, confidence interval.

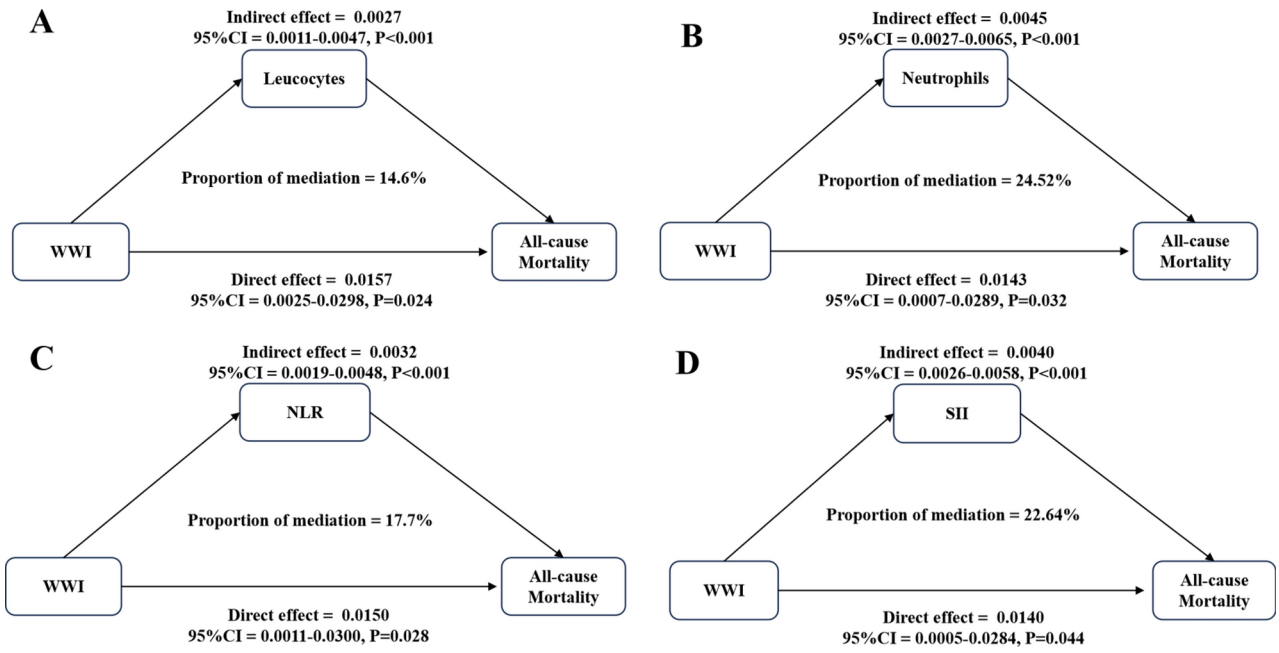

Fig. 5. Analysis of the mediation by leucocytes (**A**), neutrophils (**B**), NLR (**C**), and SII (**D**)of the associations of WWI with all-cause mortality. WWI, weight-adjusted waist circumference index. NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Data availability

The data used in this study are publicly available from the CDC's NHANES and NDI databases. Corresponding authors will make datasets available upon reasonable request.

Received: 15 October 2024; Accepted: 3 March 2025
Published online: 12 March 2025

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Acknowledgements
We acknowledge the NHANES and NDI databases for data provision and all participants involved.

Author contributions
HW ,YL and ZW designed the study. HZ, ZX and XL collected the data. HW, JW and WC performed the analysis. All authors contributed to the writing and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This study was conducted using de-identified data from the NHANES, which is publicly available and exempt from ethical approval as per the CDC guidelines. No additional consent was required for this retrospective analysis.

Additional information
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