Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Sleep disturbance heightened the association of the system inflammation response index with all-cause mortality among type 2 diabetes patient: a cross-sectional study

**Simeng Feng**
The First Affiliated Hospital of Jinan University
**Zerui You**
The First Affiliated Hospital of Jinan University
**Jiyang Pan**
jiypan@vip.163.com

The First Affiliated Hospital of Jinan University

**Research Article**

**Keywords:** Sleep disturbance, Mortality, National Health and Nutrition Examination Survey, NHANES, T2D, Systemic inflammation response index, SIRI

**Posted Date:** November 23rd, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-11365301/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** No competing interests reported.

# Sleep disturbance heightened the association of the system inflammation response index with all-cause mortality among type 2 diabetes patient: a cross-sectional study


## Author list:

**Simeng Feng[1 #], Zerui You[1 #], Jiyang Pan[1 *]**

[1] Department of Psychiatry, Sleep Medicine Center, The First Affiliated Hospital of Jinan University, Guangzhou 510632, P.R. China

[#] Equal contributions.

[*] Corresponding author: **Ji Yang Pan, M.D., Department of Psychiatry, Sleep Medicine Centre, First Affiliated Hospital of Jinan University, Guangzhou, Guangdong Province, 510632, P.R. China.**

**E-mail:** jiypan@vip.163.com



## Abstract

**Background:** The systemic inflammation response index (SIRI) has been identified as a novel inflammatory marker for various diseases. However, its impact on all-cause mortality among patients with type 2 diabetes (T2D) remains unclear. In this prospective cohort study, we aim to investigate the association between SIRI and all-cause mortality in individuals with T2D and to evaluate the interaction between sleep disturbance and SIRI.

**Methods:** Data were collected from the National Health and Nutrition Examination Survey (NHANES) conducted between 2005 and 2018. Vital status records were obtained from the National Death Index (NDI). Multivariable Cox

regression analyses were performed to estimate the associations between SIRI, all-cause mortality, and cardiovascular disease (CVD) mortality. Stratified analyses and interaction tests were conducted to assess the interaction between SIRI and sleep disturbance on all-cause mortality.

**Result:** A total of 5,012 adults with T2D were included. Compared with the second quartile (Q2), the highest quartile of SIRI (Q4) was associated with a significantly higher risk of all-cause mortality (HR: 1.84, 95% CI: 1.54–2.20) and CVD mortality (HR: 1.55, 95% CI: 1.04–2.32). Restricted cubic spline (RCS) analysis revealed an L-shaped association between SIRI and all-cause mortality. Interaction tests showed that the relationship between SIRI and all-cause mortality was more pronounced in individuals with sleep disturbance than in those without, indicating that sleep disturbance may modify this association.

**Limitations:** First, the observational study design precludes causal inference. Second, baseline SIRI measurements may not reflect long-term inflammatory status. Finally, potential biases cannot be entirely excluded.

**Conclusion:** SIRI exhibits an L-shaped association with all-cause mortality among T2D patients, and this association is significantly exacerbated by the presence of sleep disturbance.

**Keywords:** Sleep disturbance; Mortality; National Health and Nutrition Examination Survey, NHANES; T2D; Systemic inflammation response index, SIRI.

# 1 INTRODUCTION

Diabetes mellitus is a group of carbohydrate metabolism disorders characterized

by elevated blood glucose levels due to insufficient utilization and excessive production of glucose [1]. According to the International Diabetes Federation (IDF), approximately 10.5% of the global population had diabetes in 2021, and this figure is projected to rise to 12.2% by 2045, affecting 783 million individuals, with type 2 diabetes (T2D) accounting for up to 90% of cases[2, 3]. Extensive research has demonstrated that diabetes, particularly T2D, is a significant risk factor for cardiovascular disease (CVD) and is associated with an increased risk of all-cause and CVD-specific mortality compared to the general population[4-7]. According to the National Vital Statistics Reports (NVSR), diabetes was among the top ten leading causes of death in the United States in 2021, with a 2.4% increase compared to 2020[8]. The rising prevalence and mortality rates make diabetes one of the leading chronic non-communicable diseases globally, posing a substantial threat to human health. Research on T2D has identified inflammation as a critical etiological factor[9]. Chronic low-grade inflammation is implicated in the onset and progression of T2D, with inflammatory biomarkers, such as cytokines, contributing to an increased risk of disease [10-13]. However, evidence regarding the predictive role of chronic inflammation in adverse cardiovascular outcomes in T2D patients remains limited.

The systemic inflammation response index (SIRI) is a novel inflammatory biomarker that has been increasingly studied in various chronic diseases. For instance, elevated SIRI levels have been associated with cognitive impairment[14], and a growing body of evidence suggests its relevance in the prognosis of multiple cancers, such as pancreatic [15], breast [16], colorectal [17], cervical[18], oral [19], and lung cancer[20]. Studies

by Zhang et al. have shown that high SIRI levels predict an increased risk of gestational diabetes, adverse pregnancy outcomes [21, 22], and T2D complications [23]. Evidence from NHANES studies has further corroborated these findings [24, 25]. Collectively, these studies suggest a potential relationship between SIRI and T2D, influencing its prognosis. However, the specific mechanisms underlying these associations remain unclear, necessitating further investigation.

Patients with diabetes are prone to insomnia, which is both a risk factor for diabetes and a contributor to complications and mortality. Approximately 77% of individuals with T2D frequently experience insomnia symptoms, such as difficulty initiating and maintaining sleep[26, 27]. Sleep disturbance is a significant risk factor for diabetes, comparable to traditional risk factors [28, 29]. Research indicates that sleep deprivation reduces insulin sensitivity[30, 31], whereas extending sleep duration can improve it [32]. Meta-analyses have shown that insomnia is associated not only with an increased risk of T2D and poor glycemic control[33, 34] but also with higher rates of cardiovascular complications and mortality [35, 36].

Both sleep disturbance and elevated SIRI are linked to adverse outcomes in T2D, but their combined effects remain unclear. Therefore, we conducted this study to investigate the association between SIRI and all-cause mortality in T2D patients and to determine whether sleep disturbance modifies this relationship.

# 2 METHODS

## 2.1 Study population

We analysed publicly available data from the 2005-2018 cycles of the National

Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC). Informed consent was obtained in writing from all participants. For further information regarding the NHANES initiative, please refer to the Centers for Disease Control and Prevention website.

The analysis was then limited to 2005-2018 NHANES participants with diabetes, defined as a self-reported physician diagnosis, fasting plasma glucose ≥ 7.0 mmol/L, or HbA1c ≥ 6.5% [37, 38]. Exclusion criteria included: 1) possible individuals with type 1 diabetes (defined as those aged < 20 years who used only insulin); 2) participants with missing information on survival status (3), SIRI (146), PHQ-9 (104), sleeping data (20), and covariates (139 for education level, 722 for PIR; 109 for BMI; 4 for smoking; 581 for drinking). In total, 5012 patients with type 2 diabetes were included in this study population (Fig 1).

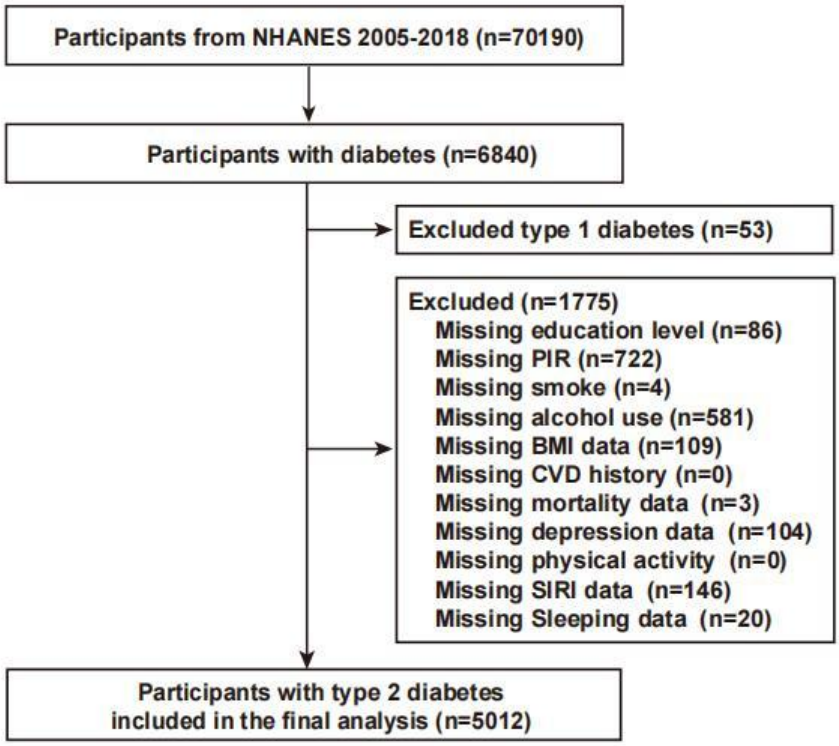



**Figure 1**. Flowchart of participants included in this study.

Note: NHANES, National Health and Nutrition Examination Survey; PIR, family poverty income ratio; BMI, body mass index; CVD, cardiovascular disease.

## 2.2 Assessment of Sleep Disturbance

Sleep disturbance was derived from a single NHANES sleep item, in which respondents are asked whether they have ever reported difficulty sleeping to a physician or other health professional. Response categories were yes, no, refused and don't know; an affirmative answer identified participants with sleep disturbance, whereas refused and don't know answers were treated as missing data.

## 2.3 Assessment of SIRI

Blood samples from NHANES participants were collected and analyzed at the Mobile Examination Centers (MEC) employing a Beckman Coulter HMX Hematology Analyzer. Lymphocyte, neutrophil, monocyte, and platelet counts were measured via complete blood count and were presented as $\times 10^3$ cells/ml. The SIRI level was calculated using the formula: monocyte count ×neutrophil count/lymphocyte count. In this study, SIRI was regarded as a primary exposure variable due to its potential relevance in indicating systemic inflammatory processes.

## 2.4 Mortality outcomes of the study

The outcomes were all-cause mortality and CVD mortality. Mortality outcomes were obtained from the 2019 public-use NHANES Linked Mortality Files provided by the National Center for Health Statistics (NCHS), which link NHANES participants to death records from the National Death Index (NDI) (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). Participants were followed from the baseline examination until death or 31 December 2019, whichever occurred first. Deaths with

an underlying cause coded as I00–I09, I11, I13, I20–I51, or I60–I69 under the International Classification of Diseases, 10th Revision (ICD-10), were classified as CVD mortality. All-cause mortality encompassed all deaths, irrespective of the underlying cause.

## 2.5 Covariates

Covariates for model adjustment were obtained from the NHANES interview and examination data and covered demographic, socioeconomic, lifestyle, and health-related factors. Age at interview was entered as a continuous variable. Other adjustment factors included sex, race/ethnicity, marital status, body mass index, and the variables defined below.

Lifestyle factors comprised alcohol consumption, smoking status, and leisure-time physical activity. Alcohol consumption was recorded as a binary variable (yes/no). Leisure-time activity was obtained from the interviewer-administered Global Physical Activity Questionnaire. Weekly activity time was expressed in moderate-equivalent minutes by multiplying vigorous activity minutes by two and adding moderate activity minutes. Participants reporting no activity, >0 to ≤150 min/week, or >150 min/week were classified as inactive, insufficiently active, or sufficiently active, respectively[39]. Smoking categories combined lifetime cigarette consumption with current smoking behaviour: fewer than 100 cigarettes indicated never smoking; at least 100 cigarettes with no current smoking indicated former smoking; and at least 100 cigarettes with daily or occasional current smoking indicated current smoking.

Socioeconomic circumstances were characterized by the poverty income ratio and

148 educational attainment. The poverty income ratio was divided into three intervals: < 1.3,
149 1.3-3.49, and ≥ 3.5. Education was coded on a five-level scale, ranging from less than
150 ninth grade to ninth–eleventh grade, high school graduation, some college education or
151 an Associate of Arts degree, and college graduation or above.

152 A history of CVD or stroke was identified from participants' reports of a
153 diagnosis by a healthcare professional or their use of prescription medications for the
154 respective condition. Depressive symptoms were assessed with the Patient Health
155 Questionnaire-9 (PHQ-9), with a total score of 10 or higher indicating their presence[40].

156 ## 2.6 Statistical Analysis

157 Analysis of variance and chi-square tests were used for statistical comparisons.
158 Kaplan-Meier curves illustrated survival across SIRI groups in participants with
159 diabetes, with differences evaluated using the log-rank test.

160 Cox proportional hazards regression was used to examine the associations of SIRI
161 with all-cause and CVD mortality. Covariate adjustment was introduced progressively:
162 no adjustment in the crude model, adjustment for demographic factors in Model I, and
163 further adjustment for CVD history and stroke history in Model II. Restricted cubic
164 spline (RCS) regression characterized the shape of these associations. The candidate
165 specifications placed three knots at the 10th, 50th, and 90th percentiles; four knots at
166 the 5th, 35th, 65th, and 95th percentiles; or five knots at the 5th, 27.5th, 50th, 72.5th,
167 and 95th percentiles. Knot selection was based on the Akaike information criterion
168 (AIC). Trends across SIRI quartiles were assessed using a trend test.

169 The potential interaction between sleep disturbance and SIRI in relation to all-

cause mortality was examined through stratified analyses, RCS regression, and multiplicative interaction terms. Sensitivity analyses incorporated sampling weights following the NHANES analytical guidelines[41]. A combined 14-year fasting subsample MEC weight was obtained by dividing the corresponding 2-year weight by seven. Analyses were performed in R version 4.4.1, with $P < 0.05$ indicating statistical significance.

# 3 RESULTS

## 3.1 Population characteristics

Table 1 presents the demographic characteristics based on SIRI quartiles of 5012 participants with diabetes from NHANES 2005-2018. The participants had a median age of 62.0 years, and 52.8% were male. Of the total participants, 1,768 (35.3%) were classified as having sleep disturbances. Those exhibiting elevated SIRI were more likely to be male, non-Hispanic white, engage in current drinking and smoking, have lower physical activity levels, and were also more likely to have a higher BMI, a history of CVD, and stroke.

**Table 1.** Characteristics of participants with T2D based on SIRI concentrations.

| Variables | Total (*N*=5012) | Quartile 1 (*n*=1255) | Quartile 2 (*n*=1253) | Quartile 3 (*n*=1252) | Quartile 4 (*n*=1252) | Statistics *p* |
|---|---|---|---|---|---|---|
| Age (years) | 62.0 (52.0-71.0) | 60.0 (51.0-67.0) | 61.0 (51.0-69.0) | 62.0 (52.0-72.0) | 66.0 (56.0-75.0) | 0.111 |
| Gender, n (%) | | | | | | **<0.001** |
| Male | 2648 (52.8%) | 532 (42.4%) | 596 (47.6%) | 723 (57.7%) | 797 (63.7%) | |

| Variables | Total (*N*=5012) | Quartile 1 (*n*=1255) | Quartile 2 (*n*=1253) | Quartile 3 (*n*=1252) | Quartile 4 (*n*=1252) | Statistics *p* |
|---|---|---|---|---|---|---|
| Female | 2364 (47.2%) | 723 (57.6%) | 657 (52.4%) | 529 (42.3%) | 455 (36.3%) | |
| BMI (kg/m2) | 31.3 (27.4-36.6) | 30.7 (27.0-35.5) | 31.6 (27.8-36.7) | 31.4 (27.6-36.7) | 31.6 (27.5-37.6) | **<0.001** |
| Education, n (%) | | | | | | 0.085 |
| Less Than 9th Grade | 818 (16.3%) | 221 (17.6%) | 206 (16.4%) | 218 (17.4%) | 173 (13.8%) | |
| 9-11th Grade | 815 (16.3%) | 228 (18.2%) | 212 (16.9%) | 178 (14.2%) | 197 (15.7%) | |
| High School Grad/GED | 1204 (24.0%) | 292 (23.3%) | 298 (23.8%) | 300 (24.0%) | 314 (25.1%) | |
| Some College or AA degree | 1369 (27.3%) | 325 (25.9%) | 332 (26.5%) | 344 (27.5%) | 368 (29.4%) | |
| College Graduate or above | 806 (16.1%) | 189 (15.1%) | 205 (16.4%) | 212 (16.9%) | 200 (16.0%) | |
| Marry status, n (%) | | | | | | 0.177 |
| Marry/Living with partner | 3021 (60.3%) | 725 (57.8%) | 758 (60.5%) | 775 (61.9%) | 763 (60.9%) | |
| Widowed/Divorced/Separated/Never married | 1991 (39.7%) | 530 (42.2%) | 495 (39.5%) | 477 (38.1%) | 489 (39.1%) | |
| Race, n (%) | | | | | | **<0.001** |
| Non-Hispanic White | 1834 (36.6%) | 242 (19.3%) | 395 (31.5%) | 517 (41.3%) | 680 (54.3%) | |
| Non-Hispanic Black | 1289 (25.7%) | 526 (41.9%) | 332 (26.5%) | 240 (19.2%) | 191 (15.3%) | |
| Mexican American | 911 (18.2%) | 238 (19.0%) | 257 (20.5%) | 250 (20.0%) | 166 (13.3%) | |
| Other Hispanic | 499 (10.0%) | 117 (9.3%) | 140 (11.2%) | 124 (9.9%) | 118 (9.4%) | |

| Variables | Total (*N*=5012) | Quartile 1 (*n*=1255) | Quartile 2 (*n*=1253) | Quartile 3 (*n*=1252) | Quartile 4 (*n*=1252) | Statistics *p* |
|---|---|---|---|---|---|---|
| Other Race/multiracial | 479 (9.6%) | 132 (10.5%) | 129 (10.3%) | 121 (9.7%) | 97 (7.7%) | |
| PIR | 1.8 (1.0-3.4) | 1.7 (1.0-3.4) | 1.9 (1.0-3.4) | 1.8 (1.0-3.5) | 1.8 (1.1-3.4) | 0.830 |
| Drinking status, n (%) | | | | | | **<0.001** |
| Yes | 3405 (67.9%) | 807 (64.3%) | 820 (65.4%) | 870 (69.5%) | 908 (72.5%) | |
| No | 1607 (32.1%) | 448 (35.7%) | 433 (34.6%) | 382 (30.5%) | 344 (27.5%) | |
| Smoking status, n (%) | | | | | | **<0.001** |
| Never smoker | 2501 (49.9%) | 726 (57.8%) | 685 (54.7%) | 569 (45.4%) | 521 (41.6%) | |
| Former smoker | 1706 (34.0%) | 340 (27.1%) | 397 (31.7%) | 476 (38.0%) | 493 (39.4%) | |
| Current smoker | 805 (16.1%) | 189 (15.1%) | 171 (13.6%) | 207 (16.5%) | 238 (19.0%) | |
| Depressive symptom, n (%) | | | | | | **0.005** |
| Yes | 618 (12.3%) | 127 (10.1%) | 144 (11.5%) | 166 (13.3%) | 181 (14.5%) | |
| No | 4394 (87.7%) | 1128 (89.9%) | 1109 (88.5%) | 1086 (86.7%) | 1071 (85.5%) | |
| Physical activity, n (%) | | | | | | **<0.001** |
| Inactive | 3509 (70.0%) | 821 (65.4%) | 849 (67.8%) | 895 (71.5%) | 944 (75.4%) | |
| Insufficiently active | 663 (13.2%) | 172 (13.7%) | 172 (13.7%) | 162 (12.9%) | 157 (12.5%) | |
| Sufficiently active | 840 (16.8%) | 262 (20.9%) | 232 (18.5%) | 195 (15.6%) | 151 (12.1%) | |
| CVD history, n (%) | | | | | | **<0.001** |
| Yes | 871 (17.4%) | 142 (11.3%) | 171 (13.6%) | 252 (20.1%) | 306 (24.4%) | |

| Variables | Total (*N*=5012) | Quartile 1 (*n*=1255) | Quartile 2 (*n*=1253) | Quartile 3 (*n*=1252) | Quartile 4 (*n*=1252) | Statistics *p* |
|---|---|---|---|---|---|---|
| No | 4141 (82.6%) | 1113 (88.7%) | 1082 (86.4%) | 1000 (79.9%) | 946 (75.6%) | |
| Stroke history, n (%) | | | | | | **<0.001** |
| Yes | 415 (8.3%) | 97 (7.7%) | 70 (5.6%) | 111 (8.9%) | 137 (10.9%) | |
| No | 4597 (91.7%) | 1158 (92.3%) | 1183 (94.4%) | 1141 (91.1%) | 1115 (89.1%) | |
| Sleep disturbance, n (%) | | | | | | **0.001** |
| Yes | 1768 (35.3%) | 416 (33.1%) | 417 (33.3%) | 434 (34.7%) | 501 (40.0%) | |
| No | 3244 (64.7%) | 839 (66.9%) | 836 (66.7%) | 818 (65.3%) | 751 (60.0%) | |

Notes: Bold p-values denote statistically significance at the $p < 0.05$ level. The specific range for the SIRI quantiles: Quartile 1 [0, 0.74]; Quartile 2 (0.74, 1.13]; Quartile 3 (1.13, 1.70]; Quartile 4 (1.70, 20.4].

SIRI, systemic inflammatory response index; BMI, body mass index; PIR, family poverty income ratio; CVD, cardiovascular disease.

## 3.2 Associations of the SIRI with mortality

Among the 5,012 participants with diabetes in the study cohort, 977 deaths were documented, including 180 CVD-related deaths, over an average follow-up period of 6.7 years. As illustrated in Fig. 2, Kaplan-Meier analysis indicated that individuals in the highest quartile (Q4) of SIRI exhibited significantly elevated all-cause ($P < 0.001$) and cardiovascular ($P = 0.031$) mortality compared to those in quartile 2 (Q2) and quartile 3 (Q3). This disparity progressively intensified over the course of the follow-up period. Following multivariable adjustment, the adjusted multivariate hazard ratios

(HRs) and corresponding 95% confidence intervals (CIs) for all-cause mortality were as follows: Q1 0.85 (0.69 - 1.05), Q3 1.01 (0.83 - 1.22), and Q4 1.84 (1.54 - 2.20) (P for trend < 0.001), with quartile 2 (Q2) of SIRI as the reference (Table 2). For cardiovascular mortality, the multivariable-adjusted HRs (95% CIs) were Q1 0.63 (0.39 - 1.03), Q2 reference, Q3 0.86 (0.56 - 1.33), and Q4 1.55 (1.04 - 2.32) (P for trend < 0.001). The RCS analysis elucidated the associations between SIRI and all-cause (P nonlinear < 0.0001) and cardiovascular (P nonlinear = 0.1458) mortality (Fig. 3). The findings revealed a nearly monotonic positive correlation between SIRI and both all-cause and cardiovascular mortality.

**Table 2.** Multivariate cox regression analysis examining the associations between SIRI and mortality of participants with T2D.

| Group | Quartile 1 | | Quartile 2 | Quartile 3 | | Quartile 4 | | P for trend |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P*-value | | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | |
| **All-cause mortality** | | | | | | | | |
| **Death/Total** | 210/1255 | | 186/1253 | 236/1252 | | 345/1252 | | |
| **Crude Model** | 0.78 (0.63 - 0.96) | **0.020** | 1[Ref.] | 1.22 (1.01 - 1.47) | 0.044 | 2.61 (2.20 - 3.10) | **<0.001** | **<0.001** |
| **Model 1** | 0.85 (0.69 - 1.05) | 0.132 | 1[Ref.] | 1.02 (0.84 - 1.24) | 0.812 | 1.87 (1.57 - 2.24) | **<0.001** | **<0.001** |
| **Model 2** | 0.85 (0.69 - 1.05) | 0.133 | 1[Ref.] | 1.01 (0.83 - 1.22) | 0.925 | 1.84 (1.54 - 2.20) | **<0.001** | **<0.001** |
| **Cardiovascular mortality** | | | | | | | | |
| **Death/Total** | 39/1255 | | 27/1253 | 54/1252 | | 60/1252 | | |
| **Crude Model** | 0.63 (0.39 - 1.01) | 0.056 | 1[Ref.] | 1.00 (0.65 - 1.53) | 0.994 | 2.01 (1.37 - 2.95) | **<0.001** | **<0.001** |

| Group | Quartile 1 | | Quartile 2 | Quartile 3 | | Quartile 4 | | P for trend |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P*-value | | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | |
| **Model 1** | 0.64 (0.39 - 1.03) | 0.065 | 1[Ref.] | 0.88 (0.58 - 1.36) | 0.575 | 1.61 (1.08 - 2.40) | **0.020** | **<0.001** |
| **Model 2** | 0.63 (0.39 - 1.03) | 0.064 | 1[Ref.] | 0.86 (0.56 - 1.33) | 0.501 | 1.55 (1.04 - 2.32) | **0.031** | **<0.001** |

Note: Hazard ratios for all-cause mortality were estimated with Cox proportional hazards models, and cause-specific mortality was additionally examined in competing-risk analyses. Estimates are presented without adjustment, and after two progressively adjusted models. Model 1 includes age, sex, race, BMI group, poverty income ratio, education, smoking status, drinking status, marital status, physical activity and depressive symptom; Model 2 additionally includes histories of cardiovascular disease and stroke. Bold values indicate P < 0.05.

Abbreviation: HR, Hazard Ratio; CI, confidence interval; BMI: Body mass index; CVD, cardiovascular disease.

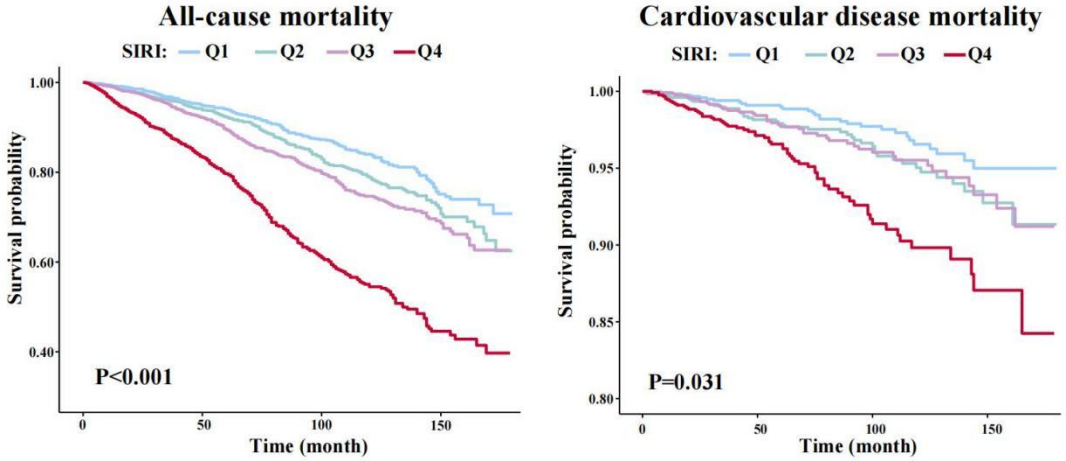



**Figure 2**. Kaplan-Meier survival curves by SIRI quartile for all-cause and cardiovascular mortality in participants with T2D.

Note: Kaplan-Meier survival curves for all-cause mortality (left) and cardiovascular disease mortality (right) by SIRI quartile in adults with type 2 diabetes. P values were calculated using the log-rank test. SIRI, systemic inflammation response index; Q1-Q4, first to fourth quartiles.

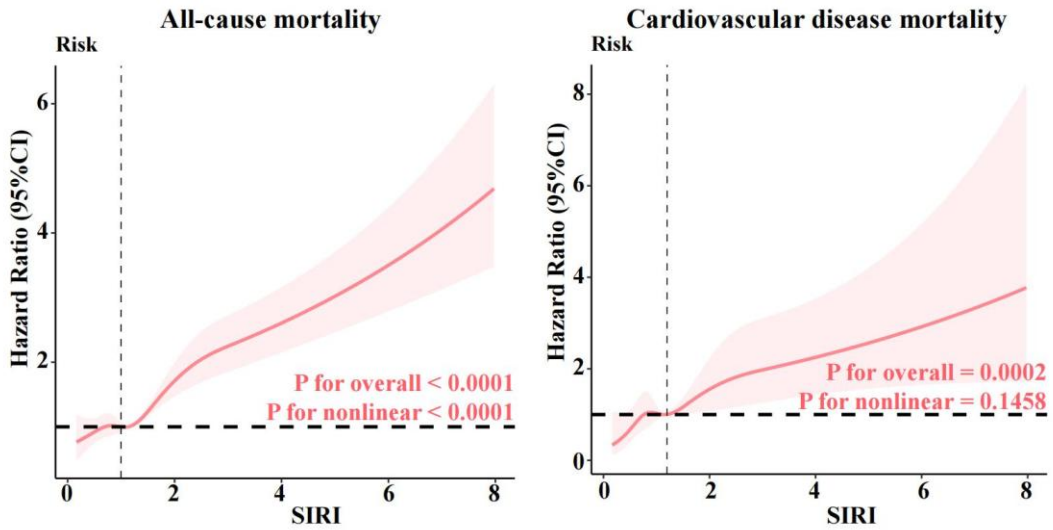



**Figure 3**. Restricted cubic spline associations of SIRI with all-cause and cardiovascular mortality.

Note: Restricted cubic spline associations of SIRI with all-cause mortality (left) and cardiovascular disease mortality (right) in adults with type 2 diabetes. Solid lines indicate adjusted hazard ratios, and shaded areas represent 95% confidence intervals. Horizontal dashed lines indicate a hazard ratio of 1, and vertical dashed lines mark the reference SIRI value. Models were adjusted for age, sex, race/ethnicity, BMI, poverty income ratio, education, smoking status, drinking status, marital status, physical activity, depressive symptoms, cardiovascular disease history, and stroke history. P values for overall and nonlinear associations are shown. SIRI, systemic inflammation response index; BMI, body mass index.

## 3.3 Effect of sleep disturbance on the relationship between SIRI and all-cause mortality among diabetes patients

There is a significant interplay between sleep disturbance and SIRI concerning all-cause mortality among diabetes patients, as shown in Table 3 (P for interaction = 0.010). Among participants with sleep disturbance, the adjusted hazard ratios (aHRs) (95% CI) for all-cause mortality were as follows: Q1 0.92 (0.63 - 1.34), Q3 1.21 (0.86 - 1.71), and Q4 2.17 (1.59 - 2.96), with Q2 of SIRI as the reference. In participants without depression, using Q2 of SIRI as the reference, the adjusted hazard ratios (aHRs) (95% CI) were as follows: Q1 0.81 (0.63 - 1.06), Q3 0.92 (0.73 - 1.16), and Q4 1.71 (1.37 - 2.13). An L-shaped relationship between SIRI and all-cause mortality (P nonlinear = 0.0024) was observed in the sleep disturbance cohort, as demonstrated in the RCS

analysis (Fig. 4). In contrast, no significant non-linear relationship was identified between SIRI and all-cause mortality in the non-sleep disturbance group.

The synergistic effects of SIRI and sleep disturbance on all-cause mortality in individuals with diabetes are illustrated in Fig. 4. Using the SIRI Q2 + non-sleep disturbance group as the reference, we observed a notably higher risk of all-cause mortality in the SIRI Q4 + sleep disturbance group (HR: 1.84, 95% CI: 1.45-2.34), whereas a reduction in mortality risk was evident in the SIRI Q1 + sleep disturbance group (HR: 0.83, 95% CI: 0.60-1.15) (Fig. 5). These findings indicate that sleep disturbance substantially potentiates the association between elevated SIRI levels and all-cause mortality in the diabetic population.

**Table 3.** The affection of sleep disturbance on the associations between SIRI and all-cause mortality of participants with T2D.

| Group | Quartile 1 | | Quartile 2 | Quartile 3 | | Quartile 4 | | P for trend | P for interaction |
|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P*-value | | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | | |
| **n/N** | 210/1255 | | 186/1253 | 236/1252 | | 345/1252 | | | |
| **Sleep disturbance** | | | | | | | | | **0.010** |
| **Yes** | 0.92 (0.63 - 1.34) | 0.655 | 1[Ref.] | 1.21 (0.86 - 1.71) | 0.272 | 2.17 (1.59 - 2.96) | **<0.001** | **<0.001** | |
| **No** | 0.81 (0.63 - 1.06) | 0.122 | 1[Ref.] | 0.92 (0.73 - 1.16) | 0.480 | 1.71 (1.37 - 2.13) | **<0.001** | **<0.001** | |

Note: Model was adjusted for age, sex, race, BMI, poverty income ratio group, education, smoking status, drinking status, marital status, physical activity and depressive symptom, CVD history, and stroke history. Bold p-values denote statistically significance at the $p < 0.05$ level.

Abbreviation: HR, Hazard Ratio; CI, confidence interval; BMI: Body mass index; CVD, cardiovascular disease.

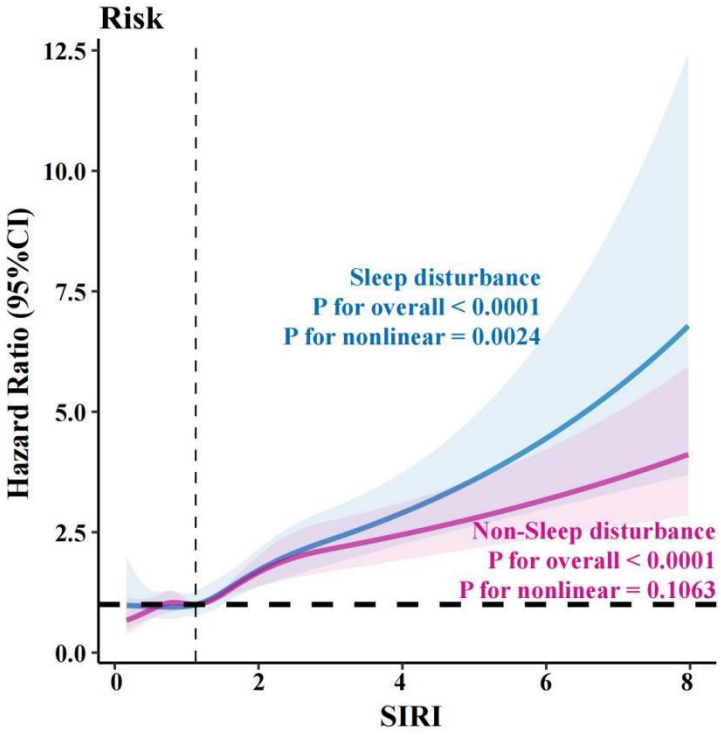



**Figure 4**. The relationship of SIRI with all-cause mortality of participants with T2D according to sleep disturbance.

Note: Restricted cubic spline associations between SIRI and all-cause mortality in adults with type 2 diabetes, stratified by sleep disturbance. Blue and purple lines represent adjusted hazard ratios for participants with and without sleep disturbance, respectively; shaded areas indicate 95% confidence intervals. The horizontal dashed line indicates a hazard ratio of 1, and the vertical dashed line marks the reference SIRI value. Models were adjusted for age, sex, race/ethnicity, BMI, poverty income ratio, education, smoking status, drinking status, marital status, physical activity, depressive symptoms, cardiovascular disease history, and stroke history. P values for overall and nonlinear associations are shown for each group. SIRI, systemic inflammation response index; BMI, body mass index.

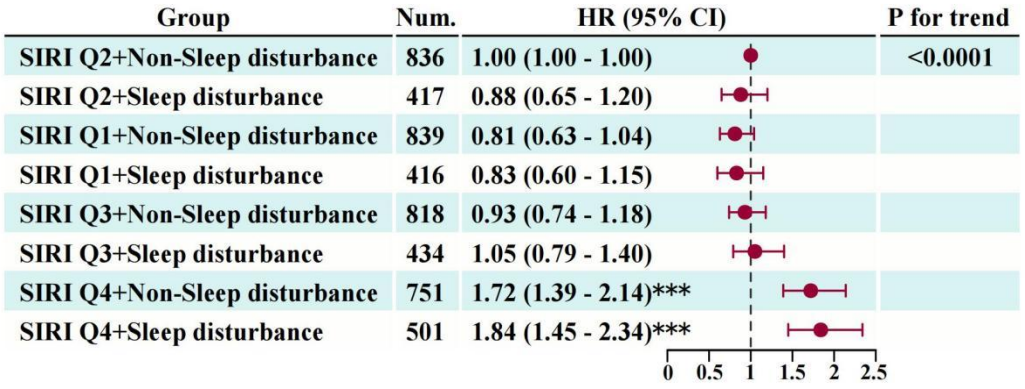



**Figure 5**. The interactive effects of SIRI and sleep disturbances on all-cause mortality of participants with T2D.

Note: Joint associations of SIRI quartiles and sleep disturbance with all-cause mortality in adults with type 2 diabetes. Participants in SIRI Q2 without sleep disturbance served as the reference group.

Points and horizontal error bars represent adjusted hazard ratios and 95% confidence intervals, respectively; the vertical dashed line indicates a hazard ratio of 1. Models were adjusted for age, sex, race/ethnicity, BMI, poverty income ratio, education, smoking status, drinking status, marital status, physical activity, depressive symptoms, cardiovascular disease history, and stroke history. Num., number of participants; HR, hazard ratio; CI, confidence interval; SIRI, systemic inflammation response index; Q1-Q4, first to fourth quartiles; BMI, body mass index. ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$.

# 4 DISCUSSION

In this study based on a large, nationally representative sample of U.S. adults with T2D, we found a significant association between SIRI and mortality. Individuals in the highest SIRI quartile exhibited higher all-cause mortality and CVD-specific mortality compared to those in the second quartile. When SIRI was analyzed as a continuous variable, we observed an L-shaped relationship with all-cause mortality and a linear association with CVD-specific mortality. Furthermore, we identified a combined effect of sleep disturbance and SIRI on all-cause mortality in T2D patients, with sleep disturbance amplifying the association between SIRI and mortality. These findings suggest that SIRI may serve as a potential biomarker for identifying subgroups of T2D patients with sleep disturbance who are at higher risk for poor prognosis.

Globally, T2D is a leading cause of death and disability, contributing significantly to the burden of disease [9]. Emerging evidence links chronic low-grade inflammation to the onset and progression of T2D [42]. However, further research is needed to identify biomarkers related to T2D prognosis. To our knowledge, this is the first study to investigate the combined effects of SIRI and sleep disturbance on mortality in the T2D population.

As a novel inflammatory biomarker, SIRI integrates monocyte, neutrophil, and lymphocyte counts into a comprehensive assessment system. It is a straightforward,

accessible, and cost-effective indicator of chronic low-grade inflammation. SIRI has been associated with mortality across various diseases. For example, Zhang et al. reported that elevated SIRI levels predict higher all-cause mortality in stroke patients [43], and in individuals with chronic kidney disease, higher SIRI levels were linked to increased mortality [44]. Additionally, a cohort study involving 85,154 participants found that high SIRI levels were associated with increased risks of CVD subtypes, such as ischemic stroke, hemorrhagic stroke, and myocardial infarction [45]. In our current NHANES-based study of T2D patients, we observed an L-shaped relationship between SIRI and all-cause mortality, as well as a linear relationship with CVD-specific mortality.

The underlying mechanisms linking SIRI to mortality in T2D patients may involve inflammation and immune responses. T2D is characterized by insulin resistance [46, 47], and cellular stress responses that drive insulin resistance—such as endoplasmic reticulum stress, specific lipid deposition, and lipotoxicity—can trigger chronic low-grade inflammation through innate immune responses. [48, 49]. Neutrophils, the most abundant type of white blood cell, are markers of subclinical inflammation and are widely implicated in the pathogenesis of T2D [50-52]. Animal studies have shown that during the early stages of high-fat-diet feeding, neutrophils accumulate in visceral adipose tissue [53]. Neutrophils release interleukin-1β (IL-1β) and neutrophil elastase (NE), which induce insulin resistance by impairing insulin signaling and degrading insulin receptor substrate-1 (IRS-1)[54, 55]. In T2D patients, abnormally activated neutrophils can form structures known as neutrophil extracellular traps (NETs), which

328 consist of DNA modified with cytosolic, granular, and nuclear proteins [56]. While the
329 role of NETs in T2D pathogenesis remains debated, they have been identified as key
330 contributors to T2D-related complications, such as diabetic foot ulcers [57], diabetic
331 nephropathy [58], and diabetic retinopathy[59]. Lymphocytes, major components of
332 adaptive immunity, have also been implicated in T2D. Recent studies have
333 demonstrated causal relationships between $CD8^+$ T-cell counts, $CD4^+CD8^-$ T-cell
334 counts, and T2D susceptibility[60]. Meta-analyses have revealed imbalances between
335 Th17 and Treg cells in T2D patients, with increased Th17 cell percentages and
336 decreased Treg cell levels [61]. Additionally, abnormal distribution of circulating B-cell
337 subsets has been observed in T2D patients, characterized by increased
338 $CD19^+CD24^+CD27^+$ cells and $CD19^+CD24^+CD38^+$ cells, the latter of which is
339 associated with metabolic parameters such as the triglyceride-glucose (TyG) index,
340 High-density lipoprotein (HDL), and cholesterol levels[62]. Monocytes are key
341 participants in chronic inflammation, and elevated circulating monocyte counts are
342 associated with a higher risk of T2D [60]. It is believed that macrophages are the
343 predominant immune cell type among all metabolic organs. Most resident macrophages,
344 which are independent of monocytes, persist throughout embryonic development [63].
345 Additionally, a subset of macrophages can be derived from monocytes in response to
346 inflammatory stimuli[64]. Increased macrophage infiltration in pancreatic islets has been
347 observed in human T2D patients [65], and macrophages have been shown to regulate
348 islet angiogenesis and β-cell proliferation in mouse models [66, 67], supporting the role
349 of monocytes in T2D development. Moreover, T2D is commonly associated with

overweight and visceral obesity. In obese rats, white adipose tissue (WAT) secretes pro-inflammatory tumor necrosis factor-alpha (TNF-α), altering insulin sensitivity. Macrophages, the most abundant non-adipocyte cell type in WAT, constitute up to 40-50% of WAT cells in obese individuals, further implicating monocytes in T2D pathogenesis[68-71].

In our stratified analysis of sleep disturbance in T2D patients, we observed that sleep disturbance amplified the association between SIRI and all-cause mortality. Restricted cubic spline (RCS) analysis and interaction analysis further indicated that sleep disturbance affected T2D prognosis and modified the impact of SIRI on all-cause mortality. Sleep disturbance is highly prevalent among T2D patients, with insomnia (39%), obstructive sleep apnea (55-86%), and restless legs syndrome (8-45%) being the most common conditions[72]. Obesity and gastrointestinal symptoms are significant risk factors for sleep disturbance in T2D patients [72, 73]. Sleep disturbance, in turn, complicates T2D management, increases the likelihood of comorbidities, and accelerates disease progression [35, 74, 75]. The bidirectional relationship between sleep disturbance and T2D suggests that coexisting sleep disturbance symptoms may adversely affect T2D prognosis. In this study, T2D patients with sleep disturbance had a higher mortality risk than those without sleep disturbance, particularly among individuals with higher SIRI levels. This finding highlights the importance of managing sleep disturbance in the healthcare of T2D patients.

The present study has several strengths. First, the use of a large, nationally representative NHANES sample enhances the generalizability of our findings to the

U.S. population. Second, the availability of long-term follow-up data and sufficient mortality records from the National Death Index enabled robust investigations. Third, SIRI incorporates three types of immune and inflammation-related cells, reducing interference from intercellular interactions compared to traditional inflammatory markers like the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR). Furthermore, SIRI is inexpensive and convenient to measure, facilitating replication and application of our findings in larger samples and diverse populations. Finally, adjustments for confounding factors and additional sensitivity and subgroup analyses affirmed the robustness of our results.

However, several limitations must be acknowledged. First, the observational design precludes definitive conclusions about causality and the influence of unmeasured confounders. Second, SIRI was derived from a single baseline blood test, which does not capture long-term immune and inflammatory dynamics. Third, factors such as T2D severity, treatment during follow-up, and other unmeasured confounders remain unknown and may have influenced the outcomes. Lastly, as all information was self-reported, potential biases cannot be excluded.

## 5 Conclusion

In summary, using a nationally representative sample of U.S. T2D patients, we observed an L-shaped association between SIRI and mortality, with sleep disturbance amplifying this relationship. These findings suggest that SIRI, as a low-cost and convenient biomarker of systemic inflammation, could serve as a stratification tool to identify subgroups of T2D patients at higher risk of adverse outcomes, particularly

those with coexisting sleep disturbance. Further large-scale studies are warranted to confirm these findings and elucidate the underlying mechanisms.

## 6 List of abbreviations

| Abbreviations | Full name |
|---|---|
| SIRI | Systemic Inflammation Response Index |
| T2D | Type 2 Diabetes |
| NHANES | National Health and Nutrition Examination Survey |
| NDI | National Death Index |
| CVD | Cardiovascular Disease |
| RCS | Restricted Cubic Spline |
| HR | Hazard Ratio |
| CI | Confidence Interval |
| aHR | Adjusted Hazard Ratio |
| BMI | Body Mass Index |
| PIR | Poverty Income Ratio |
| PHQ-9 | Patient Health Questionnaire-9 |
| MEC | Mobile Examination Center |
| ICD-10 | International Classification of Diseases, 10th Revision |
| AA | Associate of Arts |
| AIC | Akaike Information Criterion |
| NLR | Neutrophil-to-Lymphocyte Ratio |
| MLR | Monocyte-to-Lymphocyte Ratio |
| IL-1β | Interleukin-1β |
| NE | Neutrophil Elastase |
| NETs | Neutrophil Extracellular Traps |
| IRS-1 | Insulin Receptor Substrate-1 |
| TNF-α | Tumor Necrosis Factor-alpha |
| WAT | White Adipose Tissue |
| TyG | Triglyceride-Glucose Index |

| | |
|---|---|
| HDL | High-Density Lipoprotein |

# 7 Declarations

## 7.1 Ethics approval and consent to participate

The study protocol (Protocol Number: Protocol #2011–17 and Protocol #2018–01) was approved by the NCHS Research Ethics Review Board (ERB) and all participants provided written informed consent prior to participation. **(**https://www.cdc.gov/nchs/nhanes/irba98.htm**).**

## 7.2 Consent for publication

All the patients have agreed to participate in this study and have also agreed to disclose their identity information. **(**https://www.cdc.gov/nchs/nhanes/irba98.htm**).**

## 7.3 Availability of data and materials

All relevant data are described within the paper. The NHANES data used in the current manuscript can be downloaded from CDC website: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx**.**

## 7.4 Competing interests

The authors have no actual or potential conflicts of interest to declare.

## 7.5 Funding

This work was funded by National Key R&D Program of China (Grant No.: 2022YFC2503902), and Guangzhou Key Laboratory for Germ-free animals and Microbiota Application (Grant No.: 202201020381).

## 7.6 Authors' contributions

Simeng Feng: Conceptualization, Methodology, Writing-original draft, Writing-

review & editing. Zerui You: Data extraction, Statistical analysis, Writing-review & editing. Jiyang Pan: Conceptualization, Funding acquisition, Investigation, Supervision, Project administration. All authors have read and agreed to the published version of the manuscript.

# 8 References


[1] SACKS D B, ARNOLD M, BAKRIS G L, et al. Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus [J]. Diabetes Care, 2023, 46(10): e151-e99.

[2] SUN H, SAEEDI P, KARURANGA S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045 [J]. Diabetes Res Clin Pract, 2022, 183: 109119.

[3] ZHENG Y, LEY S H, HU F B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications [J]. Nat Rev Endocrinol, 2018, 14(2): 88-98.

[4] MARTIN S S, ADAY A W, ALMARZOOQ Z I, et al. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association [J]. Circulation, 2024, 149(8): e347-e913.

[5] MORRISH N J, WANG S L, STEVENS L K, et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes [J]. Diabetologia, 2001, 44 Suppl 2: S14-21.

[6] TANCREDI M, ROSENGREN A, SVENSSON A M, et al. Excess Mortality among Persons with Type 2 Diabetes [J]. N Engl J Med, 2015, 373(18): 1720-32.

[7] WU H X, CHU T Y, IQBAL J, et al. Cardio-cerebrovascular Outcomes in MODY, Type 1

Diabetes, and Type 2 Diabetes: A Prospective Cohort Study [J]. J Clin Endocrinol Metab, 2023, 108(11): 2970-80.

[8] XU J, MURPHY S L, KOCHANEK K D, et al. Mortality in the United States, 2021 [J]. NCHS Data Brief, 2022, (456): 1-8.

[9] Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021 [J]. Lancet, 2023, 402(10397): 203-34.

[10] EGUCHI K, NAGAI R. Islet inflammation in type 2 diabetes and physiology [J]. J Clin Invest, 2017, 127(1): 14-23.

[11] FADAEI R, BAGHERI N, HEIDARIAN E, et al. Serum levels of IL-32 in patients with type 2 diabetes mellitus and its relationship with TNF-α and IL-6 [J]. Cytokine, 2020, 125: 154832.

[12] WANG X, BAO W, LIU J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis [J]. Diabetes Care, 2013, 36(1): 166-75.

[13] DONATH M Y, SHOELSON S E. Type 2 diabetes as an inflammatory disease [J]. Nat Rev Immunol, 2011, 11(2): 98-107.

[14] WANG X, LI T, LI H, et al. Association of Dietary Inflammatory Potential with Blood Inflammation: The Prospective Markers on Mild Cognitive Impairment [J]. Nutrients, 2022, 14(12).

[15] QI Q, ZHUANG L, SHEN Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy [J]. Cancer, 2016, 122(14): 2158-67.

[16] ZHANG S, CHENG T. Prognostic and clinicopathological value of systemic inflammation

response index (SIRI) in patients with breast cancer: a meta-analysis [J]. Ann Med, 2024, 56(1): 2337729.

[17] CAO Y, ZHENG X, HU Y, et al. Levels of systemic inflammation response index are correlated with tumor-associated bacteria in colorectal cancer [J]. Cell Death Dis, 2023, 14(1): 69.

[18] BRUNO M, BIZZARRI N, TEODORICO E, et al. The potential role of systemic inflammatory markers in predicting recurrence in early-stage cervical cancer [J]. Eur J Surg Oncol, 2024, 50(1): 107311.

[19] VALERO C, ZANONI D K, MCGILL M R, et al. Pretreatment peripheral blood leukocytes are independent predictors of survival in oral cavity cancer [J]. Cancer, 2020, 126(5): 994-1003.

[20] SHEN Y J, QIAN L Q, DING Z P, et al. Prognostic Value of Inflammatory Biomarkers in Patients With Stage I Lung Adenocarcinoma Treated With Surgical Dissection [J]. Front Oncol, 2021, 11: 711206.

[21] YILDIZ E G, TANACAN A, OKUTUCU G, et al. Can System Inflammation Response Index or Systemic Immune Inflammation Index predict gestational diabetes mellitus in the first trimester? A prospective observational study [J]. Int J Gynaecol Obstet, 2024, 166(2): 837-43.

[22] ZHANG D, ZENG Y, SUN B, et al. Inflammatory indices-Systemic Immune-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI)-during Pregnancy and Associations with Gestational Diabetes Mellitus [J]. J Inflamm Res, 2024, 17: 6521-32.

[23] SONG Y, ZHAO Y, SHU Y, et al. Combination model of neutrophil to high-density lipoprotein ratio and system inflammation response index is more valuable for predicting peripheral arterial disease in type 2 diabetic patients: A cross-sectional study [J]. Front Endocrinol (Lausanne), 2023, 14: 1100453.

[24] SI Y, CHEN Q, XIONG X, et al. The association of inflammatory biomarkers with clinical outcomes in diabetic retinopathy participants: data from NHANES 2009-2018 [J]. Diabetol Metab Syndr, 2024, 16(1): 181.

[25] LIN K, LAN Y, WANG A, et al. The association between a novel inflammatory biomarker, systemic inflammatory response index and the risk of diabetic cardiovascular complications [J]. Nutr Metab Cardiovasc Dis, 2023, 33(7): 1389-97.

[26] TAN X, VAN EGMOND L, CHAPMAN C D, et al. Aiding sleep in type 2 diabetes: therapeutic considerations [J]. Lancet Diabetes Endocrinol, 2018, 6(1): 60-8.

[27] GUPTA S, WANG Z. Predictors of sleep disorders among patients with type 2 diabetes mellitus [J]. Diabetes Metab Syndr, 2016, 10(4): 213-20.

[28] ANOTHAISINTAWEE T, REUTRAKUL S, VAN CAUTER E, et al. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis [J]. Sleep Med Rev, 2016, 30: 11-24.

[29] SHAN Z, LI Y, ZONG G, et al. Rotating night shift work and adherence to unhealthy lifestyle in predicting risk of type 2 diabetes: results from two large US cohorts of female nurses [J]. Bmj, 2018, 363: k4641.

[30] WILMS B, CHAMORRO R, HALLSCHMID M, et al. Timing Modulates the Effect of Sleep Loss on Glucose Homeostasis [J]. J Clin Endocrinol Metab, 2019, 104(7): 2801-8.

[31] SONDRUP N, TERMANNSEN A D, ERIKSEN J N, et al. Effects of sleep manipulation on markers of insulin sensitivity: A systematic review and meta-analysis of randomized controlled trials [J]. Sleep Med Rev, 2022, 62: 101594.

[32] LEPROULT R, DELIENS G, GILSON M, et al. Beneficial impact of sleep extension on fasting

insulin sensitivity in adults with habitual sleep restriction [J]. Sleep, 2015, 38(5): 707-15.

[33] JOHNSON K A, GORDON C J, CHAPMAN J L, et al. The association of insomnia disorder characterised by objective short sleep duration with hypertension, diabetes and body mass index: A systematic review and meta-analysis [J]. Sleep Med Rev, 2021, 59: 101456.

[34] KOOPMAN A D M, BEULENS J W, DIJKSTRA T, et al. Prevalence of Insomnia (Symptoms) in T2D and Association With Metabolic Parameters and Glycemic Control: Meta-Analysis [J]. J Clin Endocrinol Metab, 2020, 105(3): 614-43.

[35] HAN H, WANG Y, LI T, et al. Sleep Duration and Risks of Incident Cardiovascular Disease and Mortality Among People With Type 2 Diabetes [J]. Diabetes Care, 2023, 46(1): 101-10.

[36] HAN H, CAO Y, FENG C, et al. Association of a Healthy Lifestyle With All-Cause and Cause-Specific Mortality Among Individuals With Type 2 Diabetes: A Prospective Study in UK Biobank [J]. Diabetes Care, 2022, 45(2): 319-29.

[37] WANG S, WANG Y, WAN X, et al. Cobalamin Intake and Related Biomarkers: Examining Associations With Mortality Risk Among Adults With Type 2 Diabetes in NHANES [J]. Diabetes Care, 2022, 45(2): 276-84.

[38] KRAMER H, BOUCHER R E, LEEHEY D, et al. Increasing Mortality in Adults With Diabetes and Low Estimated Glomerular Filtration Rate in the Absence of Albuminuria [J]. Diabetes Care, 2018, 41(4): 775-81.

[39] LIAO J, HU M, IMM K, et al. Association of daily sitting time and leisure-time physical activity with body fat among U.S. adults [J]. J Sport Health Sci, 2024, 13(2): 195-203.

[40] SMOLDEREN K G, SPERTUS J A, NALLAMOTHU B K, et al. Health care insurance, financial concerns in accessing care, and delays to hospital presentation in acute myocardial

528 infarction [J]. Jama, 2010, 303(14): 1392-400.

529 [41] JOHNSON C L, PAULOSE-RAM R, OGDEN C L, et al. National health and nutrition
530 examination survey: analytic guidelines, 1999-2010 [J]. Vital Health Stat 2, 2013, (161): 1-24.

531 [42] ANTAR S A, ASHOUR N A, SHARAKY M, et al. Diabetes mellitus: Classification, mediators,
532 and complications; A gate to identify potential targets for the development of new effective
533 treatments [J]. Biomed Pharmacother, 2023, 168: 115734.

534 [43] ZHANG Y, XING Z, ZHOU K, et al. The Predictive Role of Systemic Inflammation Response
535 Index (SIRI) in the Prognosis of Stroke Patients [J]. Clin Interv Aging, 2021, 16: 1997-2007.

536 [44] HUANG P, MAI Y, ZHAO J, et al. Association of systemic immune-inflammation index and
537 systemic inflammation response index with chronic kidney disease: observational study of
538 40,937 adults [J]. Inflamm Res, 2024, 73(4): 655-67.

539 [45] JIN Z, WU Q, CHEN S, et al. The Associations of Two Novel Inflammation Indexes, SII and
540 SIRI with the Risks for Cardiovascular Diseases and All-Cause Mortality: A Ten-Year Follow-
541 Up Study in 85,154 Individuals [J]. J Inflamm Res, 2021, 14: 131-40.

542 [46] KLEIN S, GASTALDELLI A, YKI-JÄRVINEN H, et al. Why does obesity cause diabetes? [J].
543 Cell Metab, 2022, 34(1): 11-20.

544 [47] RACHDAOUI N. Insulin: The Friend and the Foe in the Development of Type 2 Diabetes
545 Mellitus [J]. Int J Mol Sci, 2020, 21(5).

546 [48] CHEN C, COHRS C M, STERTMANN J, et al. Human beta cell mass and function in diabetes:
547 Recent advances in knowledge and technologies to understand disease pathogenesis [J]. Mol
548 Metab, 2017, 6(9): 943-57.

549 [49] MASTROTOTARO L, RODEN M. Insulin resistance and insulin sensitizing agents [J].

Metabolism, 2021, 125: 154892.

[50] HUANG J, XIAO Y, ZHENG P, et al. Distinct neutrophil counts and functions in newly diagnosed type 1 diabetes, latent autoimmune diabetes in adults, and type 2 diabetes [J]. Diabetes Metab Res Rev, 2019, 35(1): e3064.

[51] PALELLA E, CIMINO R, PULLANO S A, et al. Laboratory Parameters of Hemostasis, Adhesion Molecules, and Inflammation in Type 2 Diabetes Mellitus: Correlation with Glycemic Control [J]. Int J Environ Res Public Health, 2020, 17(1).

[52] LIN Q, ZHOU W, WANG Y, et al. Abnormal Peripheral Neutrophil Transcriptome in Newly Diagnosed Type 2 Diabetes Patients [J]. J Diabetes Res, 2020, 2020: 9519072.

[53] ELGAZAR-CARMON V, RUDICH A, HADAD N, et al. Neutrophils transiently infiltrate intra-abdominal fat early in the course of high-fat feeding [J]. J Lipid Res, 2008, 49(9): 1894-903.

[54] WATANABE Y, NAGAI Y, HONDA H, et al. Bidirectional crosstalk between neutrophils and adipocytes promotes adipose tissue inflammation [J]. Faseb j, 2019, 33(11): 11821-35.

[55] TALUKDAR S, OH D Y, BANDYOPADHYAY G, et al. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase [J]. Nat Med, 2012, 18(9): 1407-12.

[56] HIDALGO A, LIBBY P, SOEHNLEIN O, et al. Neutrophil extracellular traps: from physiology to pathology [J]. Cardiovasc Res, 2022, 118(13): 2737-53.

[57] IBRAHIM I, NUERMAIMAITI Y, MAIMAITUXUN G, et al. Neutrophil Extracellular Traps (NETs) Are Associated with Type 2 Diabetes and Diabetic Foot Ulcer Related Amputation: A Prospective Cohort Study [J]. Diabetes Ther, 2024, 15(6): 1333-48.

[58] ZHENG F, MA L, LI X, et al. Neutrophil Extracellular Traps Induce Glomerular Endothelial Cell Dysfunction and Pyroptosis in Diabetic Kidney Disease [J]. Diabetes, 2022, 71(12): 2739-

572 50.

573 [59] WANG L, ZHOU X, YIN Y, et al. Hyperglycemia Induces Neutrophil Extracellular Traps
574 Formation Through an NADPH Oxidase-Dependent Pathway in Diabetic Retinopathy [J]. Front
575 Immunol, 2018, 9: 3076.

576 [60] LI J, NIU Q, WU A, et al. Causal relationship between circulating immune cells and the risk of
577 type 2 diabetes: a Mendelian randomization study [J]. Front Endocrinol (Lausanne), 2023, 14:
578 1210415.

579 [61] ZI C, HE L, YAO H, et al. Changes of Th17 cells, regulatory T cells, Treg/Th17, IL-17 and IL-
580 10 in patients with type 2 diabetes mellitus: a systematic review and meta-analysis [J].
581 Endocrine, 2022, 76(2): 263-72.

582 [62] MENDEZ-FRAUSTO G, ROMERO-AGUILERA G, SANCHEZ-GUTIERREZ R, et al. B
583 regulatory cells associated with changes in biochemical and inflammatory parameters in
584 normal-glycemic individuals, pre-diabetes and T2DM patients [J]. Diabetes Res Clin Pract,
585 2021, 173: 108692.

586 [63] HASHIMOTO D, CHOW A, NOIZAT C, et al. Tissue-resident macrophages self-maintain
587 locally throughout adult life with minimal contribution from circulating monocytes [J].
588 Immunity, 2013, 38(4): 792-804.

589 [64] GUILLIAMS M, SCOTT C L. Liver macrophages in health and disease [J]. Immunity, 2022,
590 55(9): 1515-29.

591 [65] WU M, LEE M Y Y, BAHL V, et al. Single-cell analysis of the human pancreas in type 2 diabetes
592 using multi-spectral imaging mass cytometry [J]. Cell Rep, 2021, 37(5): 109919.

593 [66] CHITTEZHATH M, GUNASEELAN D, ZHENG X, et al. Islet macrophages are associated

with islet vascular remodeling and compensatory hyperinsulinemia during diabetes [J]. Am J Physiol Endocrinol Metab, 2019, 317(6): E1108-e20.

[67] YING W, LEE Y S, DONG Y, et al. Expansion of Islet-Resident Macrophages Leads to Inflammation Affecting β Cell Proliferation and Function in Obesity [J]. Cell Metab, 2019, 29(2): 457-74.e5.

[68] HOTAMISLIGIL G S, SHARGILL N S, SPIEGELMAN B M. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance [J]. Science, 1993, 259(5091): 87-91.

[69] WEISBERG S P, MCCANN D, DESAI M, et al. Obesity is associated with macrophage accumulation in adipose tissue [J]. J Clin Invest, 2003, 112(12): 1796-808.

[70] HARMAN-BOEHM I, BLÜHER M, REDEL H, et al. Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the comorbidities of obesity [J]. J Clin Endocrinol Metab, 2007, 92(6): 2240-7.

[71] BLÉRIOT C, DALMAS É, GINHOUX F, et al. Inflammatory and immune etiology of type 2 diabetes [J]. Trends Immunol, 2023, 44(2): 101-9.

[72] SCHIPPER S B J, VAN VEEN M M, ELDERS P J M, et al. Sleep disorders in people with type 2 diabetes and associated health outcomes: a review of the literature [J]. Diabetologia, 2021, 64(11): 2367-77.

[73] MINAMIDA M, OKADA H, HAMAGUCHI M, et al. Association between gastrointestinal symptoms and insomnia in patients with type 2 diabetes: The KAMOGAWA-DM cohort study [J]. J Diabetes Investig, 2024, 15(7): 946-52.

[74] LIU J, RICHMOND R C, BOWDEN J, et al. Assessing the Causal Role of Sleep Traits on

Glycated Hemoglobin: A Mendelian Randomization Study [J]. Diabetes Care, 2022, 45(4): 772-81.

[75] JEON B, LUYSTER F S, SEREIKA S M, et al. Comorbid obstructive sleep apnea and insomnia and its associations with mood and diabetes-related distress in type 2 diabetes mellitus [J]. J Clin Sleep Med, 2022, 18(4): 1103-11.

# 7 Figure legends

**Figure 1. Flowchart of participants included in this study.**

Note: NHANES, National Health and Nutrition Examination Survey; PIR, family poverty income ratio; BMI, body mass index; CVD, cardiovascular disease.

**Figure 2. Kaplan-Meier survival curves by SIRI quartile for all-cause and cardiovascular mortality in participants with diabetes.**

Note: Kaplan-Meier survival curves for all-cause mortality (left) and cardiovascular disease mortality (right) by SIRI quartile in adults with type 2 diabetes. P values were calculated using the log-rank test. SIRI, systemic inflammation response index; Q1-Q4, first to fourth quartiles.

**Figure 3. Restricted cubic spline associations of SIRI with all-cause and cardiovascular mortality.**

Note: Restricted cubic spline associations of SIRI with all-cause mortality (left) and cardiovascular disease mortality (right) in adults with type 2 diabetes. Solid lines indicate adjusted hazard ratios, and shaded areas represent 95% confidence intervals. Horizontal dashed lines indicate a hazard ratio of 1, and vertical dashed lines mark the reference SIRI value. Models were adjusted for age, sex, race/ethnicity, BMI, poverty

income ratio, education, smoking status, drinking status, marital status, physical activity, depressive symptoms, cardiovascular disease history, and stroke history. P values for overall and nonlinear associations are shown. SIRI, systemic inflammation response index; BMI, body mass index.

**Figure 4. The relationship of SIRI with all-cause mortality of participants with diabetes according to sleep disturbance.**

Note: Restricted cubic spline associations between SIRI and all-cause mortality in adults with type 2 diabetes, stratified by sleep disturbance. Blue and purple lines represent adjusted hazard ratios for participants with and without sleep disturbance, respectively; shaded areas indicate 95% confidence intervals. The horizontal dashed line indicates a hazard ratio of 1, and the vertical dashed line marks the reference SIRI value. Models were adjusted for age, sex, race/ethnicity, BMI, poverty income ratio, education, smoking status, drinking status, marital status, physical activity, depressive symptoms, cardiovascular disease history, and stroke history. P values for overall and nonlinear associations are shown for each group. SIRI, systemic inflammation response index; BMI, body mass index.

**Figure 5. The interactive effects of SIRI and sleep disturbances on all-cause mortality of participants with diabetes.**

Note: Joint associations of SIRI quartiles and sleep disturbance with all-cause mortality in adults with type 2 diabetes. Participants in SIRI Q2 without sleep disturbance served as the reference group. Points and horizontal error bars represent adjusted hazard ratios and 95% confidence intervals, respectively; the vertical dashed line indicates a hazard

ratio of 1. Models were adjusted for age, sex, race/ethnicity, BMI, poverty income ratio, education, smoking status, drinking status, marital status, physical activity, depressive symptoms, cardiovascular disease history, and stroke history. Num., number of participants; HR, hazard ratio; CI, confidence interval; SIRI, systemic inflammation response index; Q1-Q4, first to fourth quartiles; BMI, body mass index. ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx