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# *BMI and Systemic Inflammation Mediating the Gender-Specific Association between Food Insecurity and Circadian Syndrome in US Adults: A Cross-sectional Study from the NHANCE*

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***ABSTRACT***

**Background:** This study aimed to investigate gender-specific associations between food insecurity (FI) and circadian syndrome (CircS) among US adult, and to explore whether body mass index (BMI) and systemic inflammation [white blood cell (WBC) count] mediate these associations. **Methods:** Cross-sectional data from 12, 601 participants (≥20 yers) in the National Health and Nutrition Examination Survey (NHANES) 2005–2016 survey were analyzed. FI was assessed using the United States Department of Agriculture food security scale module. CircS was defined as the presence of ≥4 of the following components: central obesity, hypertension, elevated fasting glucose, reduced HDL-C, elevated triglycerides, short sleep duration, and depressive symptoms. Finally, weighted logistic regression and mediation analyses were performed to evaluate associations between FI and CircS, and the mediating roles of BMI and WBC count. **Results:** FI was significantly associated with increased odds of CircS [Adjusted odds ratio (AOR)]: 1.46; 95% confidence interval [CI]: 1.26–1.70), particularly among women (AOR: 1.69; 95% CI: 1.39–2.05). BMI and WBC count partially mediated this relationship in women, accounting for 37.5% and 18.6% of the total effect, respectively. **Conclusions:** The findings highlight the role of metabolic and inflammatory dysregulation, particularly among women, as potential mechanisms linking FI and circadian health disturbances. Targeting FI through public health strategies that address these pathways may reduce the burden of CircS and related condition, and support the integration of circadian health into nutrition and chronic disease prevention policies.

## Introduction

Food insecurity (FI), defined as the inability to afford adequate nutrition for a healthy life, has become a critical public health concern worldwide. In 2022, an estimated 12.8% of U.S. households

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experienced FI for the entire year, meaning they did not always have enough food for all members (Rabbitt *et al.*, 2023). This proportion represented a statistically significant increase compared to 10.2% in 2021 and 10.5% in 2020 (Rabbitt *et al.*, 2023). Mounting evidence suggests that FI is associated with adverse health outcomes, including mental health disorders, depression, and chronic conditions such as diabetes, hypertension, and hyperlipidemia (Gundersen and Ziliak, 2015, Laraia, Silverman *et al.*, 2015). Furthermore, FI often results in poor dietary choices (Hazzard *et al.*, 2020, Morales and Berkowitz, 2016), which lead to compromised metabolic health, especially metabolic syndrome (MetS) (Garaulet and Madrid, 2010, Giugliano *et al.*, 2006, Messiah *et al.*, 2024). While the relationship between FI and MetS has been previously explored, emerging interest has focused on circadian syndrome (CircS), a novel construct integrating both metabolic and behavioral disturbances (Cherbuin *et al.*, 2019).

CircS is an expanded framework that includes all traditional MetS components (e.g., central obesity, dyslipidemia, elevated blood pressure, and impaired glucose regulation) along with short sleep duration and depressive symptoms. This integrated model reflects the multidimensional nature of health risks, particularly in socially vulnerable populations. CircS may serve as a more sensitive indicator of cumulative stress and physiological disruption compared to MetS alone (Shi *et al.*, 2022, Shi *et al.*, 2021, Zimmet *et al.*, 2019).

Existing literature suggests that FI may affect metabolic health and CircS through several pathways. FI promotes weight gain through dietary imbalances and has been significantly associated with obesity, particularly in females (Hernandez *et al.*, 2017, Morales and Berkowitz, 2016, Sharpe *et al.*, 2016). In addition, chronic nutritional deprivation and psychological stress were linked to FI (Chiu *et al.*, 2024, Garaulet and Madrid, 2010, Kirkpatrick and Tarasuk, 2008, Myers, 2020), which may amplify pro-inflammatory responses(Gowda *et al.*, 2012, Parlak Baskurt and Yardımcı, 2024), leading to disrupted metabolic functions in adipose tissue (Wang and He, 2018), muscle (Tuttle *et al.*, 2020), and liver (Koyama and Brenner, 2017), thereby increasing chronic disease risk. Although both FI and CircS have been individually linked to poor health outcomes, few studies have investigated their direct association. Moreover, the biological mechanisms connecting FI to CircS remain poorly understood. FI may trigger adverse metabolic effects through poor diet quality and erratic eating patterns, while also activating inflammatory and stress-related pathways (Martin *et al.*, 2024). "While FI is a known risk factor for individual components of CircS, its direct association with the integrated CircS construct remains unexamined. This gap is critical given that CircS demonstrates superior predictive value for cardiovascular disease compared to metabolic syndrome alone (Garcia *et al.*, 2022). Although FI has been linked to a higher prevalence of metabolic syndrome in U.S. adults (Chen *et al.*, 2024), the biological pathways, particularly the potential mediating role of systemic inflammation alongside BMI, connecting FI to the broader CircS are not well characterized (Bauer *et al.*, 2012). Elucidating these gender-specific mechanisms is essential for understanding the etiology of CircS in vulnerable populations. Therefore, this study aimed to examine the association between FI and CircS among U.S. adults using a nationally representative sample. The authors also evaluated gender differences in this association, given prior evidence suggesting stronger effects of FI in women. In addition, the researchers conducted mediation analyses to explore the role of body mass index (BMI) and white blood cell (WBC) count as potential mediators linking FI to CircS.

## Materials and Methods

### *Study design and population*

This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) covering six continuous cycles from 2005 to 2016 (i.e., 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016). NHANES is conducted by the Centers for Disease Control and Prevention (CDC) and employs a complex, multistage probability sampling design to produce nationally representative estimates of the





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health and nutritional status of the non-institutionalized U.S. civilian population. Participants completed interviewer-administered questionnaires and underwent standardized physical examinations conducted by trained medical personnel at mobile examination centers. A randomly selected subsample also provided fasting blood samples for laboratory analysis.

**Figure 1** depicts the selection process of the study population. A total of 60, 936 participants were initially enrolled. The following exclusion criteria were applied: (1) age under 20 years (n=26756); (2) pregnancy (n=261); (3) missing data on food security (n=122); (4) not being part of the fasting subsample or with an examination weight of zero (n=20241); and (5) incomplete information on CircS components (n=955). After exclusions, 12601 participants remained for the final analysis.

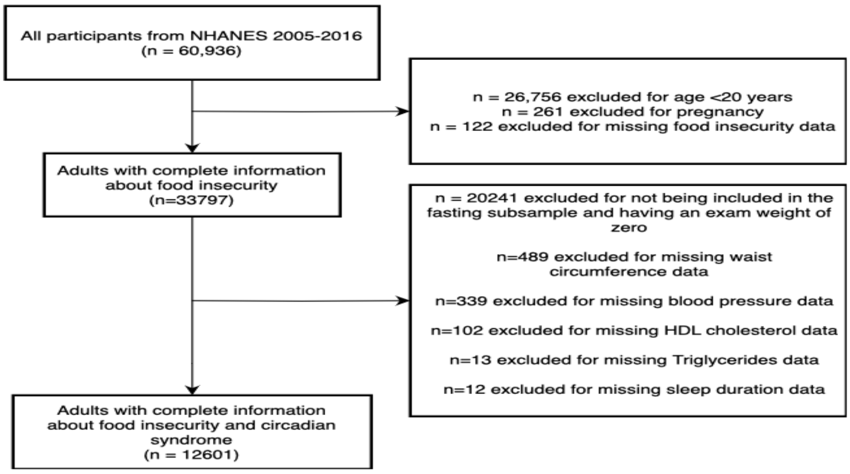


**Figure 1.** Flow chart of the participants' selection process.

***Assessment of circadian syndrome***

CircS was defined using criteria adapted from prior studies (Shi *et al.*, 2022, Shi *et al.*, 2021, Zimmet *et al.*, 2019). Specifically, it includes defining central obesity based on waist circumference data measured through physical examination (male≥102 cm/female≥88 cm); Defining blood lipid abnormalities (triglycerides≥150 mg/dl or HDL-C<40 mg/dl for males/<50 mg/dl for females) and elevated fasting blood glucose (≥100 mg/dll) using laboratory tested fasting serum data; Using standardized blood pressure measurement data (systolic blood pressure≥130 mmHg/diastolic blood pressure≥85 mmHg) to define hypertension. The above indicators all include self-reports of current medication use. The behavioral components are defined based on questionnaire data: short sleep duration (self-reported daily sleep≤6 hours) and depressive symptoms (PHQ-9 score≥10). If ≥4 out of the above 7 criteria are met, it is determined to have circadian rhythm syndrome (Xiu *et al.*, 2020).

***Assessment of food insecurity***

FI was assessed using the Food Security Survey Module included in the NHANES questionnaire, and a validated instrument developed by the United States Department of Agriculture (USDA) to evaluate household food security (FS) over the past 12 months (Bickel *et al.*, 2000). Given the focus on adults' health outcomes, only the 10 adult-relevant items (FSD032a, FSD032b, FSD032c, FSD041, FSD052, FSD061, FSD071, FSD081, FSD092, and FSD102) from the full 18-item scale were used. According to USDA guidelines, households are categorized as follows (Bickel *et al.*, 2000, Keenan *et al.*, 2001, Pinstrup-Andersen, 2009): high FS (0 affirmative responses), marginal FS (1–2 affirmative responses), low FS (3–5 affirmative responses), and very low FS (6–10 affirmative responses). The Chronbach's α for the scale ranges from 0.74 to 0.93 (Keenan *et al.*, 2001, Mohammadi *et al.*, 2012). In this study, the authors analyzed the data using the categorical FI variable as a binary variable by categorizing participants as FS (0–2 affirmative responses) or FI ($\geq$3 affirmative responses) (Gundersen and Ziliak, 2015). Consistent with USDA definitions, adults who report low or very low FS are considered to have FI (Bickel *et al.*, 2000).

### *Potential mediating variables*

To assess the extent to which FI influences CircS through intermediate pathways, several potential mediating variables were selected based on prior literature (Gowda *et al.*, 2012, Hernandez *et al.*, 2017, Morales and Berkowitz, 2016, Parlak Baskurt and Yardımcı, 2024): BMI (weight divided by height squared (kg/m$^2$)) is a relatively simple and low-cost indirect measure for assessing adiposity which provides reasonable height standardization (Nuttall, 2015). WBC count, as a classic biomarker of systemic inflammation (Cramer and Vitonis, 2017), was measured using a Beckman Coulter automated hematology analyzer employing direct current impedance method. This method automatically dilutes whole blood samples anticoagulated with ethylenediaminetetraacetic acid, and achieves accurate counting and size determination of WBC by detecting the electrical pulses generated when cells pass through micropores, as well as hemoglobin measurement using a single beam photometer (Wu *et al.*, 2021).

### *Covariates*

Demographic variables encompass age, gender (male, female), race (non-Hispanic White, non-Hispanic Black, Mexican American, Other Hispanic, Other race), family income-to-poverty ratio (≤130% federal poverty level (FPL), 130%–185% FPL, 186%–300% FPL, >300% FPL), educational level (<high school, high school diploma/GED, some college/associates degree, college graduate or above), and marital status (married or cohabit, widowed or divorced, never married). Self-reported health behaviors include inactivity or activity (no and low level, moderate and high level), alcohol consumption status (current drinker, former drinker, or never drinker), current smoking status (current smokers, former smokers, and non-smokers).

### *Ethics approval and consent to participate*

This study was performed using public data from the National Health and Nutrition Examination Survey (NHANES). The data have been de-identified and not merged or augmented in a way that has compromised the privacy of the participants. Therefore, the study requires no further approval and follows ethical guidelines. Participants' data were obtained from the publicly available NHANES, so no additional consent was obtained.

### *Data analysis*

National Center for Health Statistics analytic guidelines for analyzing NHANES data were followed. Analyses accounted for the complex sampling design of NHANES by applying appropriate sample weights (WTSAF2YR), strata, and primary sampling units. Missing data were assumed to be random based on the study's sampling structure (Shah *et al.*, 2014), with details of missing covariates provided in (**Table 1**). To address missing covariates, the authors applied multiple imputation by chained equations (MICE), generating 5 datasets to effectively manage both continuous and categorical variables while accounting for their complex interrelationships. MICE was chosen based on the missing at random (MAR) assumption, supported by the assessment of missing data patterns (Van Buuren and Groothuis-Oudshoorn, 2011). For variables that followed a normal distribution, weighted t-tests were conducted. For non-normally distributed variables, the weighted Kruskal-Wallis test was applied. Furthermore, categorical variables were compared using weighted chi-square tests. Results for normally distributed continuous variables are presented as means and standard deviations (SDs), and categorical variables are reported as weighted percentages.





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**Table 1.** Participants descriptive characteristics by FI status, NHANES 2005-2016**.**

| Variable | Overall[a] | Food security[a] | Food insecurity[a] | P-value[c] |
|---|---|---|---|---|
| Unweighted sample size | N = 12601 | N = 10316 | N = 2285 | |
| Age (y) | 47.23±16.69 | 48.07±16.79 | 41.96±15.06 | <0.001 |
| Age group (y) | | | | <0.001 |
| 20-39 | 4562 (36.2) | 3528 (34.2) | 1118 (48.9) | |
| 40-59 | 4852 (38.5) | 3992 (38.7) | 859 (37.6) | |
| 60< | 3187 (25.2) | 2796 (27.1) | 308 (13.5) | |
| Gender | | | | >0.9 |
| Female | 6401 (50.8) | 5240）(50.8) | 1163 (50.9) | |
| Male | 6200 (49.2) | 5076 (49.2) | 1122 (49.1) | |
| Race | | | | <0.001 |
| Mexican American | 1046 (8.3) | 722 (7.0) | 363 (15.9) | |
| Non-Hispanic Black | 1374 (10.9) | 1001 (9.7) | 418 (18.3) | |
| Non-Hispanic White | 8605 (68.3) | 7345 (71.2) | 1150 (50.4) | |
| Other Hispanic | 680 (5.4) | 506 (4.9) | 210 (9.2) | |
| Other Race | 896 (7.1) | 752 (7.3) | 144 (6.3) | |
| Education | | | | <0.001 |
| <High school | 2129 (16.9) | 1455 (14.1) | 791 (34.6) | |
| High school graduate | 2835 (22.5) | 2280 (22.1) | 574 (25.1) | |
| Some college | 3894 (30.9) | 3177 (30.8) | 724 (31.7) | |
| College graduate or above | 3743 (29.7) | 3404 (33.0) | 196 (8.6) | |
| Poverty-to-income ratio (% of EPL) | | | | <0.001 |
| ≤130 | 2709 (21.5) | 1671 (16.2) | 1248 (54.6) | |
| 130–185 | 1348 (10.7) | 980 (9.5) | 407 (17.8) | |
| 186–300 | 2344 (18.6) | 1950 (18.9) | 379 (16.6) | |
| 300 < | 6200 (49.2) | 5705 (55.3) | 251 (11.1) | |
| Marital status | | | | <0.001 |
| Married or partners | 8165 (64.8) | 6901 (66.9) | 1188 (52.0) | |
| Never married | 2230 (17.7) | 1712 (16.6) | 562 (24.6) | |
| Widowed or divorced | 2206 (17.5) | 1703 (16.5) | 535 (23.4) | |
| Smoking | | | | <0.001 |
| Never smoker | 6855 (54.4) | 5756 (55.8) | 1035 (45.3) | |
| Former smoker | 3150 (25.0) | 2703 (26.2) | 404 (17.7) | |
| Current smoker | 2596 (20.6) | 1847 (17.9) | 846 (37.0) | |
| Activity | | | | <0.001 |
| No and low level | 3478 (27.6) | 2744 (26.6) | 768 (33.6) | |
| Moderate and high level | 9123 (72.4) | 7572 (73.4) | 1517 (66.4) | |
| Alcohol | | | | 0.14 |
| Nondrinkers | 1424 (11.3) | 1135 (11.0) | 292 (12.8) | |
| Former drinkers | 1500 (11.9) | 1238 (12.0) | 260 (11.4) | |
| Current drinker | 9677 (76.8) | 7943 (77.0) | 1733 (75.8) | |
| Body mass index (kg/m$^{2)}$ | 28.86±6.69 | 28.69±6.55 | 29.94±7.41 | <0.001 |
| Weight status | | | | <0.001 |
| Normal weight | 3856 (30.6) | 3219 (31.2) | 622 (27.2) | |
| Overweight | 4184 (33.2) | 3476 (33.7) | 681 (29.8) | |
| Obese | 4561 (36.2) | 3621 (35.1) | 982 (43.0) | |
| WBC count (1000 cells/µl) | 6.78±2.16 | 6.68±2.09 | 7.39±2.49 | <0.001 |
| WBC count category (cells/µl) | | | | <0.001 |
| <4000 | 441 (3.5) | 371 (3.6) | 69 (3.0) | |
| 4000-10000 | 11379 (90.3) | 9388 (91.0) | 1961 (85.8) | |
| 10000< | 781 (6.2) | 557 (5.4) | 255 (11.2) | |
| Components of CircS[b] | | | | |
| Central obesity | 7057 (56.0) | 5746 (55.7) | 1314 (57.5) | 0.3 |
| Hypertension | 5923 (47.0) | 4838 (46.9) | 1092 (47.8) | 0.6 |
| Elevated plasma glucose | 3187 (49.1) | 5034 (48.8) | 1159 (50.7) | 0.3 |
| Reduced serum HDL-C | 4952 (39.3) | 3972 (38.5) | 1005 (44.0) | 0.003 |



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| | | | | |
|---|---|---|---|---|
| Elevated serum triglycerides | 4650 (36.9) | 3807 (36.9) | 848 (37.1) | >0.9 |
| Short sleep duration | 1588 (12.6) | 1186 (11.5) | 446 (19.5) | <0.001 |
| Depressive symptoms | 832 (6.6) | 505 (4.9) | 398 (17.4) | <0.001 |
| CircS | | | | 0.002 |
| No | 8896 (70.6) | 7355 (71.3) | 1515 (66.3) | |
| Yes | 3705 (29.4) | 2961 (28.7) | 770 (33.7) | |

***FS***: *Food security;* ***FI***: *Food insecurity;* ***CircS***: *Circadian syndrome;* ***FPL***: *Federal poverty level;* ***WBC***: *White blood cell;* ***HDL***: *High-density lipoprotein;* [a]: *N (%) and mean ± SD are weighted owing to the complex probability sampling of National Health and Nutrition Examination Survey data;* [b]: *Percentage of participants meeting each of the individual criteria for CircS;* [c]: *For variables that followed a normal distribution, weighted t-tests were conducted. For non-normally distributed variables, the weighted Kruskal-Wallis test was applied. Furthermore, categorical variables were compared using weighted chi-square tests.*

To assess the association between FI and CircS, two weighted logistic regression models were developed. The crude model was unadjusted, and adjusted model was adjusted for age, gender, race, income-to-poverty ratio, activity status, smoking status, alcohol use, educational attainment, and marital status. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Furthermore, analyses were stratified by gender to explore sex-specific vulnerabilities in the association between FI and CircS because the relationship between FI and obesity is stronger for females than it is for males (Hernandez *et al.*, 2017).

The authors adopted the model-based mediation analysis framework proposed by Tingley *et al*. to examine the mediating effects of BMI and WBC count and the constructed two models (Tingley *et al.*, 2014). One involved a weighted linear regression model for mediator, conditioned on FI and confounders, while the other encompassed a weighted logistic regression model for CircS, conditioned on FI, mediator, and confounders. A quasi-Bayesian estimation method with 1000 iterations was used to estimate the mediating effect. Mediation was considered present if the average causal mediation effect (ACME) was significantly different from zero. Complete mediation was assumed when the direct effect (ADE) became non-significant, indicating that the mediator fully explained the total effect. Partial mediation was indicated when both indirect and direct effects were statistically significant, suggesting that the mediator accounted for part of the relationship (MacKinnon, 2012).

Additional sensitivity analyses were also performed to assess the robustness of the results. First, additional subgroups were conducted among individuals of different age-groups, races, education levels, smoking status, alcohol use, income-to-poverty ratio status and BMI status to assess the consistency of the correlation between FI and CircS across different populations. Second, the authors categorized FI into 4 levels (high, marginal, low, and very low) to examine whether there existed a dose-response relationship between increasing severity of FI and CircS. Third, they reassessed the association between FI and CircS using data without interpolation to confirm consistency. All statistical analyses were conducted using R version 4.4.2. Two-sided P-values <0.05 were considered statistically significant.

## Results

The characteristics of 12601 adults aged 20 and older are shown by FI status (**Table 1**). Of these, 50.8% were female, 68.3% were non-Hispanic white, and 18.1% were classified as FI based on USDA definitions. Compared to food-secure people, Food-insecure individuals were younger (mean age: 41.96 vs. 48.07 years, $P<0.001$), with greater representation among Mexican American and Non-Hispanic Black populations. Households with lower incomes (≤130% FPL: 54.6%) and less education (not completing high school: 34.6%) were more likely to be FI. Behavioral risk factors included higher current smoking and physical inactivity. FI was also associated with a higher prevalence of obesity (43%vs.35%, $P<0.001$), elevated WBC count, reduced HDL-C, short sleep, depression, and greater CircS prevalence (34% vs. 29%, $P = 0.002$).

The descriptive characteristics of adults are shown by CircS status (**Table 2**). A total of 32.7% (n=4124, unweighted) of the sample had CircS. Those with CircS were older (mean 56.1 vs 43.5


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P<0.001) and more often non-Hispanic White. They reported lower educational attainment, higher rates of poverty, and were more frequently widowed or divorced. Behavioral differences included greater rates of former smoking (31.5% vs 22.4%), physical inactivity (37.7% vs 23.4%), and lower current alcohol use (72.8% vs 78.5%). BMI was higher among participants with CircS, with 61.4% classified as obese compared to 25.7% without CircS. Inflammatory activity, as indicated by WBC count, was elevated in the CircS group.

**Table 2.** Participant descriptive characteristics by CircS status, NHANES 2005–2016.

| Variable | Overall[a] | No CircS[a] | CircS[a] | P-value[c] |
|---|---|---|---|---|
| Unweighted sample size | N=12601 | N=8477 | N=4124 | |
| Age (y) | 47.2±16.7 | 43.5±16.1 | 56.1±14.7 | <0.001 |
| Age group (y) | | | | <0.001 |
| 20-39 | 4562 (36.2) | 3840 (45.2) | 602 (14.6) | |
| 40-59 | 4852 (38.5) | 3128 (36.9) | 1749 (42.4) | |
| 60< | 3187 (25.3) | 1509 (17.8) | 1773 (42.9) | |
| Gender | | | | 0.7 |
| Female | 6401 (50.8) | 4298 (50.7) | 2111 (51.2) | |
| Male | 6200 (49.2) | 4179 (49.3) | 2013 (48.8) | |
| Race | | | | <0.001 |
| Mexican American | 1046 (8.3) | 737 (8.7) | 297 (7.2) | |
| Non-Hispanic Black | 1374 (10.9) | 924 (10.9) | 445 (10.8) | |
| Non-Hispanic White | 8605 (68.3) | 5680 (66.9) | 2949 (71.6) | |
| Other Hispanic | 680 (5.4) | 483 (5.7) | 198 (4.8) | |
| Other Race | 896 (7.1) | 653 (7.7) | 235 (5.7) | |
| Education | | | | <0.001 |
| <High school | 2129 (16.9) | 1280 (15.1) | 878 (21.3) | |
| High school graduate | 2835 (22.5) | 2823 (33.3) | 866 (21.0) | |
| Some college | 3894 (30.9) | 1780 (21.0) | 1068 (25.9) | |
| College graduate or above | 3743 (29.7) | 2594 (30.6) | 1312 (31.8) | |
| Poverty-to-income ratio (% of EPL) | | | | <0.001 |
| ≤130 | 6200 (49.2) | 4357 (51.3) | 1823 (44.2) | |
| 130–185 | 2709 (21.5) | 1738 (20.5) | 977 (23.7) | |
| 186–300 | 1348 (10.7) | 873 (10.3) | 478 (11.6) | |
| 300 < | 2344 (18.6) | 1509 (17.8) | 846 (20.5) | |
| Marital status | | | | <0.001 |
| Married or partners | 8165 (64.8) | 5459 (64.4) | 2722 (66.0) | |
| Never married | 2230 (17.7) | 1789 (21.1) | 384 (9.3) | |
| Widowed or divorced | 2206 (17.5) | 1229 (14.5) | 1018 (24.7) | |
| Smoking | | | | <0.001 |
| Never smoker | 6855 (54.4) | 4849 (57.2) | 1959 (47.5) | |
| Former smoker | 3150 (25.0) | 1899 (22.4) | 1299 (31.5) | |
| Current smoker | 2596 (20.6) | 1729 (20.4) | 866 (21.0) | |
| Activity | | | | <0.001 |
| No and low level | 3478 (27.6) | 1984 (23.4) | 1555 (37.7) | |
| Moderate and high level | 9123 (72.4) | 6493 (76.6) | 2569 (62.3) | |
| Alcohol | | | | <0.001 |
| Nondrinkers | 1424 (11.3) | 899 (10.6) | 520 (12.6) | |
| Former drinkers | 1500 (11.9) | 916 (10.8) | 602 (14.6) | |
| Current drinker | 9677 (76.8) | 6662 (78.5) | 3002 (72.8) | |
| Body mass index (kg/m$^2$) | 28.9±6.7 | 27.3±6.0 | 32.6±6.7 | <0.001 |
| Weight status | | | | <0.001 |
| Normal weight | 3856 (30.6) | 3348 (39.5) | 37 (9.2) | |
| Overweight | 4184 (33.2) | 2950 (34.8) | 1208 (29.3) | |
| Obese | 4561 (36.2) | 2179 (25.7) | 2537 (61.5) | |




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|---|---|---|---|---|
| WBC count (1000 cells/µl) | 6.8±2.2 | 6.5±2.1 | 7.3±2.3 | <0.001 |
| WBC count category (cells/µl) | | | | <0.001 |
| <4000 | 441 (3.5) | 356 (4.2) | 66 (1.6) | |
| 4000-10000 | 11379 (90.3) | 7723 (91.0) | 3650 (88.5) | |
| 10000< | 781 (6.2) | 398 (4.7) | 408 (9.9) | |

***CircS***: *Circadian syndrome;* ***FPL***:*Federal poverty level;* ***WBC***: *White blood cell; [a]: N (%) and mean ± SD are weighted owing to the complex probability sampling of National Health and Nutrition Examination Survey data; [c]: For variables that followed a normal distribution, weighted t-tests were conducted. For non-normally distributed variables, the weighted Kruskal-Wallis test was applied. Furthermore, categorical variables were compared using weighted chi-square tests.*

**Table 3.** Odds ratios and 95% confidence intervals of CircS and individual components by FI status, NHANES 2005–2016

| Variable | Overall | FI | Crude model | Adjusted model |
|---|---|---|---|---|
| | Unweighted N | Unweighted N | OR(95%CI) | OR(95%CI) |
| **Overall** | | | | |
| circadian syndrome | 4124 | 834 | 1.26(1.09-1.46)[b] | 1.46 (1.26-1.70)[c] |
| Central obesity | 7136 | 1350 | 1.08 (0.95-1.22) | 1.18 (1.03-1.36)[a] |
| Hypertension | 6537 | 1184 | 1.04 (0.90-1.19) | 1.32 (1.11-1.56)[b] |
| Elevated plasma glucose | 6716 | 1254 | 1.08 (0.93-1.24) | 1.24 (1.06-1.46)[b] |
| Reduced serum HDL-C | 5200 | 1034 | 1.25 (1.08-1.45)[b] | 1.27 (1.09-1.48)[b] |
| Elevated serum triglycerides | 4880 | 891 | 1.01 (0.87-1.16) | 1.22 (1.05-1.41)[b] |
| Short sleep duration | 1868 | 469 | 1.86 (1.60-2.16)[c] | 1.27 (1.10-1.48)[b] |
| Depressive symptoms | 977 | 387 | 4.05 (3.39-4.84)[c] | 2.44 (1.99-2.99)[c] |
| **Female** | | | | |
| circadian syndrome | 2128 | 503 | 1.62(1.35-1.93)[c] | 1.69 (1.39-2.05)[c] |
| Central obesity | 4378 | 930 | 1.71 (1.40-2.08)[c] | 1.54 (1.22-1.94)[c] |
| Hypertension | 3095 | 620 | 1.21 (1.02-1.44)[a] | 1.53 (1.22-1.93)[c] |
| Elevated plasma glucose | 2900 | 611 | 1.22(1.01-1.48)[a] | 1.38 (1.13-1.69)[b] |
| Reduced serum HDL-C | 2727 | 642 | 1.82(1.55-2.14)[c] | 1.54(1.32-1.81)[c] |
| Elevated serum triglycerides | 2195 | 449 | 1.17(0.98-1.41) | 1.43 (1.17-1.75)[c] |
| Short sleep duration | 926 | 242 | 1.97(1.62-2.40)[c] | 1.25 (1.01-1.55)[a] |
| Depressive symptoms | 621 | 246 | 4.07(3.27-5.06)[c] | 2.49(1.93-3.21)[c] |
| **Male** | | | | |
| circadian syndrome | 1996 | 331 | 0.96 (0.77-1.19) | 1.27 (0.98-1.64) |
| Central obesity | 2758 | 420 | 0.72 (0.61-0.86)[c] | 0.94 (0.79-1.12) |
| Hypertension | 3442 | 564 | 0.89 (0.75-1.05) | 1.16 (0.94-1.44) |
| Elevated plasma glucose | 3816 | 643 | 0.95 (0.79-1.13) | 1.13 (0.92-1.39) |
| Reduced serum HDL-C | 2473 | 392 | 0.84 (0.67-1.04) | 1.02 (0.81-1.30) |
| Elevated serum triglycerides | 2685 | 442 | 0.87(0.73-1.03) | 1.09 (0.89-1.32) |
| Short sleep duration | 942 | 227 | 1.75(1.41-2.18)[c] | 1.32 (1.06-1.64)[a] |
| Depressive symptoms | 356 | 141 | 4.11(3.00-5.62)[c] | 2.32(1.64-3.28)[c] |

***CI***: *Confidence Interval;* ***OR***: *Odds ratio;* ***FI***: *Food insecurity; Odds ratio and confidence interval are weighted owing to the complex probability sampling of National Health and Nutrition Examination Survey data; Crude model is unadjusted. Adjusted model is adjusted for poverty to income ratio, age, gender, race, educational level, marital status, alcohol use, physical activity and smoking; [a]: P<0.05; [b]: P<0.01 and [c]: P<0.001.*

The authors examined the cross-sectional relationships between FI and CircS and its individual components (**Table 3**). Adjusted logistic regression models showed that those from FI households were 46% more likely to have CircS compared with those not living in an FI household [Adjusted odds ratio (AOR)]: 1.46; 95% CI: 1.26–1.70; *P*<0.001). In addition, compared to males, the authors found that the association between FI and CircS was stronger in females (AOR:1.69; 95% CI: 1.39-2.05; *P*<0.001), particularly with central obesity, hypertension, elevated plasma



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glucose, reduced HDL-C, elevated triglycerides and depressive symptoms. In contrast, associations among males were generally weaker (AOR:1.27; 95% CI: 0.98-1.64; $P$>0.05) and not statistically significant for most components. However, short sleep duration and depressive symptoms remained significantly associated with FI in both genders

The authors, then, investigated the potential mediation of BMI and WBC count on the association between FI and risk of CircS (**Figure 2**), adjusting for age, race, education level, income-to-poverty ratio, activity status, smoking, alcohol use and marital status. Among females, BMI and WBC count were identified as statistically significant partial mediators, accounting for 37.5% and 18.6% of the total effect, respectively. In contrast, no significant mediation effects were observed in males.

Adjusted subgroup analyses were conducted to assess the consistency of the association between FI and CircS across population groups (**Figure 2**). Notably, subgroup analyses showed that the association between FI and the occurrence of CircS was stable. Higher odds were observed among those aged 60 and older. They were Mexican Americans, Non-Hispanic Whites, never and former smokers, non and current drinkers, individuals with lower education or (≤130 FPL) and (>300 FPL) income-to-poverty ratio, and those with obesity. The writers further conducted sensitivity analyses by categorizing FI into 4 levels (high, marginal, low, and very low) (**Table 4**). The result revealed a dose-response relationship between FI and CircS after adjusting for all covariates, compared to high FS, marginal, low and very low FS had significantly higher odds of CircS, with AOR of 1.34 (95% CI: 1.10–1.63; $P$<0.01), 1.49 (95% CI: 1.24–1.77; $P$<0.001), and 1.69 (95% CI: 1.32–2.15; $P$<0.001), respectively. Females with very low FS had 2-fold higher risks of CircS compared with those having high FS (AOR: 2.00; 95% CI: 1.45-2.76; $P$<0.001), whereas no significant associations were found in men across FI levels. Sensitivity analyses using data without interpolation were basically consistent with this study's main findings (**Table 5**). However, among men, marginal and low FS were associated with increased odds of CircS (AOR: 1.42; 95% CI: 1.00-2.00; $P$<0.05 and AOR: 1.48; 95% CI: 1.08-2.01; $P$<0.05, respectively), while the association disappeared in those with very low FS.

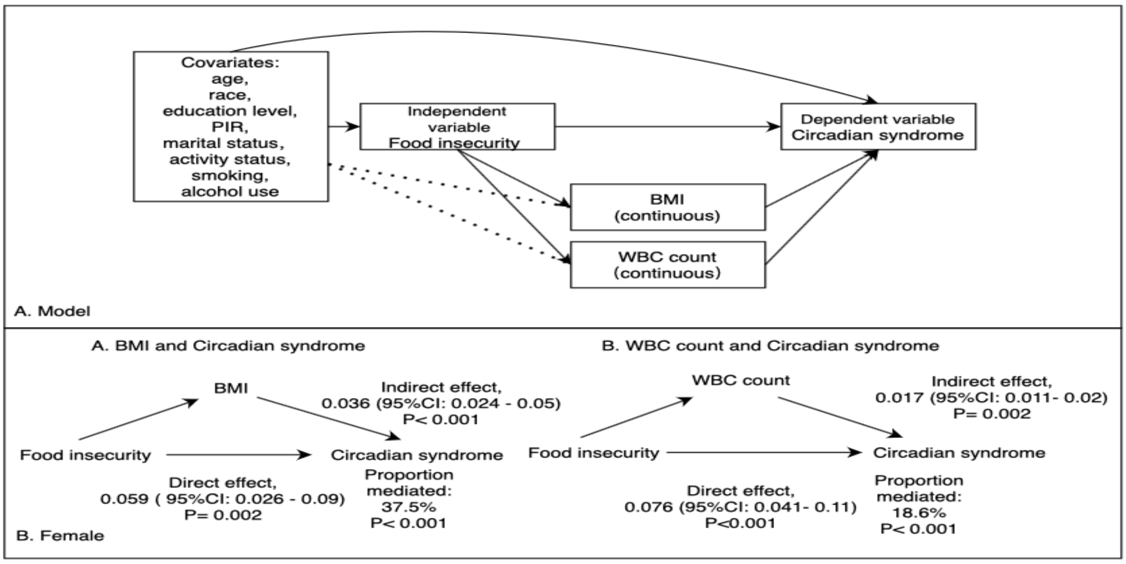


**Figure 2.** Mediating effect of BMI and WBC count on the relationship between food insecurity and CircS

*Diagram of mediation analysis results examining whether association between food insecurity (binary exposure) and CircS (binary outcome) is mediated by BMI (continuous variable) and WBC count (continuous variable). The result indicated that both BMI and WBC count significantly mediated the association in women. Solid lines indicate significant associations (P<0.05). Direct and indirect effects are presented as coefficients with 95% CIs with P values. Proportion-mediated measure is used, obtained by dividing the indirect effect by the total effect. BMI: Body Mass Index; CI: Confidence Interval; CircS: Circadian Syndrome; PIR: Income-to-poverty ratio; WBC: White blood cell.*




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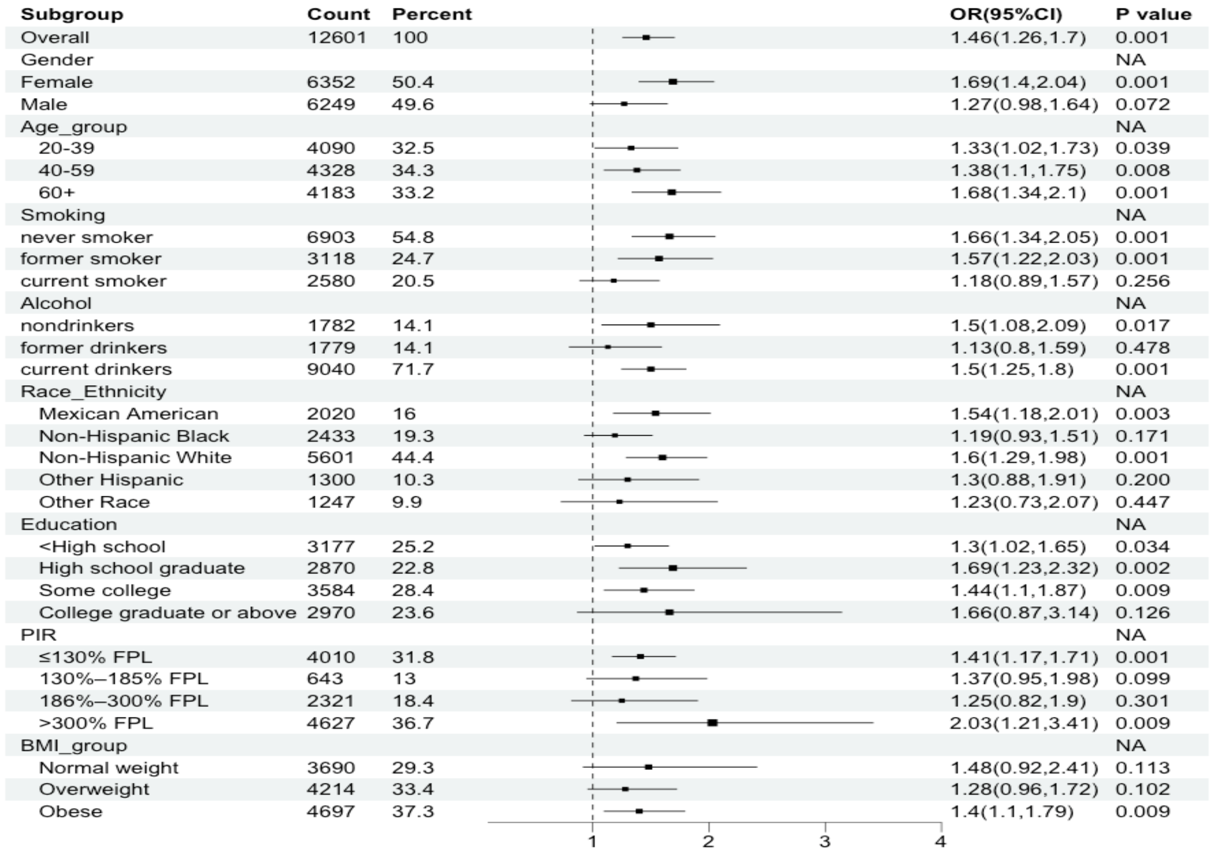


**Figure 2.** The subgroup analyses and forest plots of the association between FI and CircS.

*Logistic regression models were used to analyze subgroup analyses and forest plots of the association between FI and CircS,ratio of ratios (OR). Models adjusted for age, sex, race, education, PIR, smoking, alcohol use, marital status and physical activity. Stratification variables were not adjusted in the corresponding models.*

**Table 4.** The association between FI and CircS by categorizing food insecurity into 4 groups.

| Food security category | Crude model OR(95%CI) | Adjusted model OR(95%CI) |
|---|---|---|
| Overall | | |
| High FS | Ref | Ref |
| Marginal FS | 1.07 (0.90-1.27) | 1.34 (1.10-1.63)[b] |
| Low FS | 1.22 (1.03-1.44)[a] | 1.49 (1.24-1.77)[c] |
| Very low FS | 1.36 (1.08-1.71)[b] | 1.69 (1.32-2.15)[c] |
| Female | | |
| High FS | Ref | Ref |
| Marginal FS | 1.18 (0.93-1.50) | 1.32 (0.99-1.76) |
| Low FS | 1.53 (1.24-1.89)[c] | 1.65 (1.31-2.08)[c] |
| Very low FS | 1.85 (1.39-2.44)[c] | 2.00 (1.45-2.76)[c] |
| Male | | |
| High FS | Ref | Ref |
| Marginal FS | 0.95 (0.74-1.23) | 1.36 (0.98-1.88) |
| Low FS | 0.94 (0.73-1.21) | 1.34 (0.99-1.80) |
| Very low FS | 0.97 (0.71-1.34) | 1.40 (0.94-2.07) |

***CI***: *Confidence Interval;* ***OR***: *Odds ratio;* ***FS***: *Food security; Crude model is unadjusted. Adjusted model is adjusted for poverty to income ratio, age, gender, race, educational level, marital status, alcohol use, physical activity and smoking;* [a]: *P<0.05;* [b]: *P<0.01 and* [c]: *P<0.001.*



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**Table 5**. The association between FI and CircS using data without interpolation.

| Food security category | Crude model OR(95%CI) | Adjusted model OR(95%CI) |
|---|---|---|
| Overall | | |
| FS | Ref | Ref |
| FI | 1.26 (1.09-1.46)[b] | 1.50 (1.29-1.75)[c] |
| High FS | Ref | Ref |
| Marginal FS | 1.07 (0.90-1.27) | 1.40 (1.13-1.73)[b] |
| Low FS | 1.22 (1.03-1.44)[a] | 1.56 (1.30-1.86)[c] |
| Very low FS | 1.36 (1.08-1.71)[b] | 1.71(1.33-2.19)[c] |
| Female | | |
| FS | Ref | Ref |
| FI | 1.62(1.35-1.93)[c] | 1.68 (1.37-2.05)[c] |
| High FS | Ref | Ref |
| Marginal FS | 1.18 (0.93-1.50) | 1.36 (0.99-1.86) |
| Low FS | 1.53 (1.24-1.89)[c] | 1.65 (1.29-2.11)[c] |
| Very low FS | 1.85 (1.39-2.44)[c] | 2.05 (1.46-2.87)[c] |
| Male | | |
| FS | Ref | Ref |
| FI | 0.96 (0.78-1.19) | 1.35 (1.03-1.78)[a] |
| High FS | Ref | Ref |
| Marginal FS | 0.95 (0.74-1.23) | 1.42 (1.00-2.00)[a] |
| Low FS | 0.94 (0.73-1.21) | 1.48 (1.08-2.01)[a] |
| Very low FS | 0.97 (0.71-1.34) | 1.42 (0.94-2.12) |

***CI***: *Confidence Interval;* ***OR***: *Odds ratio;* ***FS***: *Food security; Crude model is unadjusted. Adjusted model is adjusted for poverty to income ratio, age, gender, race, educational level, marital status, alcohol use, physical activity and smoking; [a]: $P<0.05$; [b]: $P<0.01$ and [c]: $P<0.001$.*

## Discussion

This study analyzed data from the NHANES 2005–2016 survey, focusing on adults aged 20 and older. It was found that FI was significantly associated with higher odds of CircS after adjusting for demographic, socioeconomic and lifestyle factors. These associations exhibited a dose–response relationship, with the more severity of FI almost always associated with the higher odds of CircS. Moreover, the associations were stronger in females. Mediation analysis further showed that BMI and WBC count partially explained the relationship between females, accounting for 37.5% and 18.6% of the total effect, respectively.

To the best of the authors' knowledge, this is the first study to investigate the link between FI and CircS. A systematic review has shown that FI is linked to a range of adverse health outcomes, including obesity, diabetes, hypertension, hyperlipidemia, poor sleep, depression, and reduced nutrient intake (Gundersen and Ziliak, 2015). The findings add to this evidence by demonstrating a significant association between FI and CircS, even after adjusting for key confounders such as age, gender, race, and socioeconomic status. This may be due to low-quality dietary intake among people in FI, who are more inclined to choose inexpensive, calorie-dense, nutrient-poor foods and decrease intake of fruits, vegetables, and protein sources (Kirkpatrick and Tarasuk, 2008, Morales and Berkowitz, 2016, Sharpe *et al.*, 2016). The United States Dietary Guidelines recommends a balanced diet rich in fruits, vegetables, whole grains, and legumes (Phillips and safety, 2021), and this approach should lower the risk of CircS. Additionally, many individuals living with FI experiences a "feast-or-famine" cycle in which food intake oscillates according to fluctuations in food availability, including binge eating during periods of abundance and restrictive behaviors during scarcity (Dinour *et al.*, 2007, Fairburn *et al.*, 2003, Olson *et al.*, 2007). Furthermore, adults with severe FI were more



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likely to conduct compensatory behaviors (e. g. , vomiting, laxative/diuretic use, fasting, and intense exercise) compared with those with marginal FS, for the purpose of controlling weight or counteracting the effects of eating (Dhurandhar *et al.*, 2015, Hazzard *et al.*, 2020). The patterns of low-quality dietary intake, fluctuations in food availability and compensatory behaviors increase the risk of both micronutrient deficiencies and metabolic disorders (Garaulet and Madrid, 2010, Lopes *et al.*, 2023, Olson *et al.*, 2007, Solmi *et al.*, 2021). Consistent with the findings, obesity was more prevalent among those with FI. While prior NHANES-based studies have focused on MetS, CircS incorporates not only all components of MetS but also depression and sleep disorders that are also strongly associated with FI (Arenas *et al.*, 2019). Evidences show that FI is linked to chronic psychological stress (Myers, 2020), which may elevate cortisol levels and increase risk of depression, anxiety, and sleep disorders (Arenas *et al.*, 2019, Chiu *et al.*, 2024, Silverman *et al.*, 2015). Moreover, people with FI show lower adherence to medical recommendations (Boulangé *et al.*, 2016, Ogungbe *et al.*, 2024), compared to those who are FS, potentially under the economic pressure of "treat or eat" trade-off between prescription medication and household food (Boulangé *et al.*, 2016, Ogungbe *et al.*, 2024). This "treat-or-eat" dilemma has been shown to undermine disease management and heighten the risk of adverse health outcomes (Berkowitz *et al.*, 2014, Laraia, 2013).

The findings indicate that the association between FI and CircS is stronger in females than in males. Previous research on prevalence of MetS suggests that men are more likely to have elevated triglycerides, fasting glucose, and blood pressure, while women more commonly exhibit low HDL-C and abdominal obesity (Messiah *et al.*, 2024). Despite these differences, women appear to experience greater health impacts from FI. This may be due to adaptive mechanisms that prioritize fat storage in response to FI, which could support reproductive functions. Consistent with this, a recent review found no significant link between FI and obesity in men but noted a possible short-term association in women (Hernandez *et al.*, 2017, Larson and Story, 2011). Beyond physiological pathways, social factors may also play a role. Women are more likely to have lower educational attainment, lower household income, and fewer social networks and may face sociocultural pressures that may prioritize the nutritional needs of other household members, limiting their own access to adequate nutrition (Johnson *et al.*, 2018).

The association between FI and CircS in females was partially mediated by BMI or WBC count. FI was significantly associated with obesity in females (Hernandez *et al.*, 2017, Larson and Story, 2011), and obesity may contribute to metabolic dysfunction through increased release of non-esterified fatty acids (NEFAs) from adipose tissue. Excess NEFAs can promote insulin resistance and hepatic fat accumulation (Heptulla *et al.*, 2001, Jensen, 2008, Randle *et al.*, 1963), key features of metabolic disturbance. WBC count, a marker of chronic inflammation, also partially mediated the FI-CircS relationship. FI-related nutrient deficiencies, such as lower folate levels (Johnson *et al.*, 2018, Lopes *et al.*, 2023), can impair immune function and promote inflammation (Gowda *et al.*, 2012, Parlak Baskurt and Yardımcı, 2024). In addition, FI is often linked to high-fat and high-sugar diets, which reduce gut microbial diversity and alter microbial metabolite production, such as short-chain fatty acids, while increasing intestinal permeability (Soliz-Rueda *et al.*, 2025). These changes contribute to systemic inflammation and metabolic endotoxemia (Boulangé *et al.*, 2016), a correlate of chronic diseases.

Previous studies have reported a significant association between FI and MetS, particularly among women (Messiah *et al.*, 2024, Reeder and Reneker, 2024). These studies have shown that FI is related to central obesity, dyslipidemia, hypertension, and impaired glucose metabolism, with BMI frequently identified as a mediating factor in this relationship. The present study expands upon this literature by focusing on CircS, which incorporates both metabolic risk factors and additional components such as short sleep duration



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and depressive symptoms. The authors observed that FI was significantly associated with CircS, especially among women, and found that both BMI and systemic inflammation, as indicated by WBC count, partially mediated this association. Compared with MetS, CircS captures a broader array of health disturbances related to behavioral and psychological stressors. The findings suggest that FI may influence health not only through metabolic dysregulation but also via circadian and inflammatory pathways, highlighting the need for multidimensional prevention strategies that address both physical and psychosocial determinants of health.

A major strength of this study is the comprehensive consideration of many sociodemographic and lifestyle factors, allowing for an extensive characterization of the study population, adjustment of the analyses and exploration of potential mediators. Second, the use of data from NHANES, a large and nationally representative survey, enhances the generalizability of the findings. Additionally, FI was assessed using the 18-item U.S. Household Food Security Survey Module, a widely accepted gold-standard instrument in Western countries, ensuring the reliability and validity of exposure measurement(Lee and Oldham, 2017).

This study has several limitations to note. First, the use of cross-sectional surveys restricts the authors' ability to infer the directional causality association between FI and CircS (Wang and Cheng, 2020). Second, the use of cross-sectional data may introduce biases in estimating longitudinal mediation effects. Additionally, although BMI is commonly used as a measure for assessing obesity, it cannot directly measure body fat and may misclassify individuals by overestimating adiposity in athletes with high muscle mass and in patients with edema, and underestimating adiposity in sarcopenic individuals with low lean mass (Sweatt *et al.*, 2024). Third, FI was self-reported, which may introduce bias due to individual perceptions or recall inaccuracies (Tadesse *et al.*, 2020). Additionally, FI is considered a cyclic phenomenon with possible episodes of food adequacy and food shortage (Dinour *et al.*, 2007). These episodes of food adequacy and food shortage are not fully captured by the 18-item U.S. Household Food Security Survey Module, which broadly focuses on the previous 12 months.

## Conclusion

In summary, this study reveals that FI is significantly associated with increased risk of CircS among U.S. adults, with the strongest associations observed in women. These gender-specific patterns may be partially explained by elevated levels of obesity and systemic inflammation. The findings suggest that interventions targeting FI should consider both metabolic and circadian health consequences. Public health strategies that aim to reduce obesity and inflammation among food-insecure populations-particularly women-may help mitigate the development of CircS. Taken together, these findings highlight the need for integrated strategies that address the metabolic, inflammatory, and behavioral pathways linking food insecurity and circadian health-particularly in women.

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## Authors' contributions

Conceptualization was done by Su J, Ye J; Design research was carried out by Wang T, Su J; Research was conducted by Su J, Guo S, and Wang T; Data curation was conducted by Su J, Wang T, and Mo R; Su J, Guo S, and Ye J did the writing; Resources were prepared Su J, Wang H; Supervision, validation, and project administration: Ye J; Li H; Wang J. Su J bears primary responsibility for the final content. All authors read and approved the final manuscript.

## Conflict of interest

The authors declared no competing interests.

 



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