

# Association of Dietary Inflammation Index with Infertility Risk in US Women: A Cross-Sectional Analysis from NHANES (2013-2020)

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**Background:** This study investigates the relationship between the Dietary Inflammation Index (DII) and the risk of infertility among women of childbearing age in the United States.

**Methods:** This cross-sectional study analyzed data from 3184 women aged 20 to 45 years, utilizing information from the National Health and Nutrition Examination Survey (NHANES, 2013–2020). Dietary intake was assessed using 24-hour recall interviews to calculate the DII score, which is based on 28 dietary components. The DII score is used to assess the inflammatory potential of diet, with higher scores indicating a greater likelihood of inducing inflammation. Multivariate logistic regression and restricted cubic splines (RCS) were employed to evaluate the association between DII and infertility risk, adjusting for potential confounders such as age, BMI, and lifestyle factors. LASSO regression was used to identify key predictors, and a nomogram for predicting infertility risk was developed.

**Results:** Among the participants, 12.41% were classified as infertile. Women with infertility had significantly higher DII scores compared to those without infertility (2.27 [1.09, 3.14] vs 1.99 [0.92, 2.97];  $p=0.016$ ). The analysis revealed a positive association between higher DII scores and increased infertility risk, even after adjusting for confounding variables. RCS analysis indicated no significant nonlinear relationship between DII and infertility ( $p$  for non-linearity = 0.118). Furthermore, DII was identified as a more effective predictor of infertility risk than the Healthy Eating Index (HEI). The nomogram prediction model, developed from the predictive factors identified via LASSO regression, exhibited robust predictive performance, achieving an AUC of 85.1% (95% CI: 74.7%–95.5%).

**Conclusion:** A pro-inflammatory diet, indicated by a high Dietary Inflammatory Index (DII) score, is associated with an elevated risk of infertility in American women, thereby supporting dietary interventions to reduce inflammation for improved fertility outcomes and highlighting the relevance of dietary counseling in fertility care.

**Keywords:** infertility, dietary inflammation index, healthy eating index, NHANES, LASSO, nomogram model

## Introduction

Infertility, defined by the World Health Organization as the inability to achieve clinical pregnancy after 12 months or more of regular, unprotected intercourse, is a major public health issue affecting millions of families worldwide.<sup>1</sup> While infertility itself is not a specific symptom, it is often associated with reproductive health issues such as menstrual disorders, anovulation, and hormone imbalances. Global estimates show that between 1990 and 2010, 48.5 million couples experienced infertility, of which 19.2 million were primary infertility and 29.3 million were secondary infertility.<sup>2</sup> Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved.

From a societal perspective, infertility can deprive individuals of fundamental human rights, such as the right to decide the number, timing, and intervals of children they may have.<sup>3</sup> Compared to men, infertile women often experience higher psychosocial stress and are more prone to psychosocially induced mental and physical health problems, such as

anxiety and depression. Furthermore, the treatment of infertility can generate many negative emotions.<sup>2</sup> Because the primary goal becomes conception, sexual intercourse may lose its spontaneity and erotic value, potentially affecting the ability to maintain intimate sexual relations and possibly leading to sexual dysfunction. Economically, although millions of children are now born through assisted reproductive technologies such as in-vitro fertilization (IVF), this remains an expensive and difficult-to-access opportunity, especially in low- and middle-income countries.

The causes of infertility are complex and diverse, including genetic, endocrine, immune, and environmental factors. Among them, diet, as a modifiable factor, has an important impact on reproductive health.<sup>4</sup> For example, a high-fat or high-carbohydrate diet is associated with ovarian dysfunction and ovulatory disorders.<sup>5</sup> In addition, poor dietary habits may induce chronic inflammation, which in turn affects follicular development, oocyte quality, and endometrial health, further exacerbating the risk of infertility.<sup>6</sup>

In this study, we focused on two indices: the dietary inflammatory index (DII) and the healthy eating index (HEI) to evaluate their association with infertility risk. The HEI is employed to assess diet quality by evaluating whether a group of foods adheres to the Dietary Guidelines for Americans (DGA). The HEI scoring criteria have been continuously refined to evaluate both overall diet quality and individual component scores. For evaluating inflammatory diets, we utilized the DII, which was first proposed by Shivappa et al in 2014. The DII, based on a comprehensive review of published literature,<sup>7</sup> assesses the potential impact of dietary factors on the body's inflammatory state and quantifies the pro-inflammatory or anti-inflammatory potential of the diet. Higher DII scores may indicate a greater dietary pattern associated with inflammation, as the index incorporates the effects of systemic inflammatory biomarkers such as IL-1 $\beta$ , IL-4, IL-6, IL-10, TNF- $\alpha$ , and CRP. Both the DII and HEI have been extensively used to study various health issues, including cancer, cardiovascular disease, autoimmune diseases, mental health disorders, respiratory diseases, and reproductive health.<sup>8–10</sup> This widespread use underscores the importance of examining the relationship between different dietary indices and diseases<sup>11–13</sup> and highlights the potential for identifying appropriate dietary indices to aid in disease prevention and prediction, which could offer new insights for clinical treatment in the future.

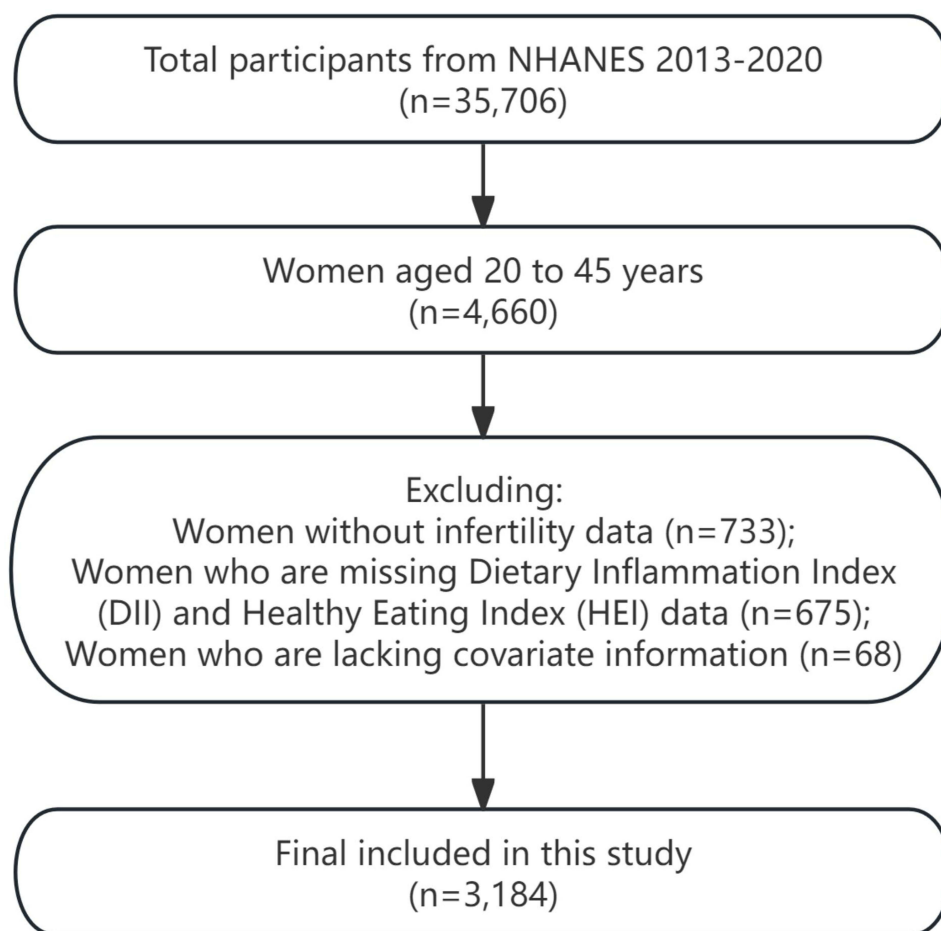
Previous studies have demonstrated a significant association between the DII and infertility risk. However, to our knowledge, few investigations have explored correlations between other dietary indicators and infertility, or compared the predictive efficacy of different indicators for infertility risk. Therefore, this study aims to utilize data from the 2013–2020 National Health and Nutrition Examination Survey (NHANES) to further examine the relationship between DII and infertility risk. Existing literature indicates that a pro-inflammatory diet may interfere with follicular development, endometrial receptivity, and hormonal balance by elevating inflammatory markers, thereby increasing the risk of infertility.<sup>14</sup> Conversely, anti-inflammatory dietary patterns (eg, diets rich in whole grains, vegetables, and fruits) may help improve the reproductive endocrine environment.<sup>15</sup> Therefore, we will employ multivariate weighted logistic regression, restricted cubic splines (RCS), and subgroup analysis to evaluate the correlation between DII and HEI, and construct a predictive model for infertility risk. This aims to provide evidence for clinical decision-making, public health policy, and individual health management.

## Methods

### Data Source and Patient Selection

The NHANES, conducted by the National Center for Health Statistics (NCHS), is an ongoing survey program that collects clinical measurements, laboratory data, and questionnaire responses from population samples. NHANES provides comprehensive information on health, nutrition, disease, and risk factors, covering various aspects such as demographic characteristics, health status, dietary intake, physical measurements, and laboratory results. This data is extensively used for research, policy development, and public health decision-making. The original research data for this study was sourced from NHANES, which can be accessed and downloaded from the official website (<https://www.cdc.gov/nchs/nhanes/index.htm>).

Infertility data was first included in the reproductive health questionnaire in 2013. Consequently, we analyzed NHANES data from 2013 to 2020, which included 35,706 participants. Our study focused on women aged 20 to 45 years ( $n=4660$ ). We excluded those without infertility data ( $n=733$ ), missing Dietary Inflammation Index (DII) and



**Figure 1** Flowchart describing the inclusion and exclusion of study participant.

Healthy Eating Index (HEI) data ( $n=675$ ), and those lacking covariate information ( $n=68$ ). This resulted in a final sample of 3184 participants (Figure 1). The Institutional Review Board of the National Center for Health Statistics reviewed and approved the project (<https://www.cdc.gov/nchs/nhanes/irba98.htm>), and written informed consent was obtained from all participants. The survey followed the ethical guidelines set forth in the Declaration of Helsinki.

## Assessment of Dietary Information

Dietary information was collected at the mobile examination center (MEC) through a 24-hour recall interview conducted by the nutrition methodology working group of NHANES. The DII was calculated using 28 dietary components following the protocol established by Shivappa et al.<sup>6</sup> Six crucial markers of systemic inflammation (IL-1 $\beta$ , IL-6, IL-4, IL-10, TNF- $\alpha$ , and CRP) were utilized to reflect inflammatory status. Each dietary component was assigned a score of “+1” if it increased CRP, TNF- $\alpha$ , IL-1, and IL-6 levels or decreased IL-4 and IL-10 levels, and a score of “-1” if it decreased CRP, TNF- $\alpha$ , IL-1, and IL-6 levels or increased IL-4 and IL-10 levels. Components with no effect on inflammatory markers were scored as “0”. To assess the inflammatory potential of each participant’s diet, individual food component-specific DII scores were aggregated into an overall DII score. A positive score indicates a pro-inflammatory potential, a negative score indicates an anti-inflammatory potential, and a score of zero indicates no significant impact on inflammation. Initially, we conducted an analysis of the DII as a continuous variable. Subsequently, participants were evenly categorized into four groups based on DII distribution: low DII (Q1:  $-3.77 \leq \text{DII} < 0.94$ ), moderate-low DII (Q2:  $0.94 \leq \text{DII} < 2.04$ ), moderate-high DII (Q3:  $2.04 \leq \text{DII} < 3.00$ ), and high DII (Q4:  $\text{DII} \geq 3.00$ ). We also calculated the HEI, a trusted measure of dietary quality that evaluates adherence to the US Dietary Guidelines

for Americans (DGA). The HEI-2020 used in our study retains the same components and scoring criteria as the HEI-2015, consisting of nine adequacy components and four moderation components, each scored from 5 to 10 points.<sup>16,17</sup> Higher HEI scores indicate better overall dietary quality, with individual component scores shedding light on different aspects of diet quality. Similar to the Dietary Inflammation Index (DII), the HEI was initially analyzed as a continuous variable and then categorized into quartiles: low HEI (Q1:  $21.10 \leq \text{DII} < 41.31$ ), moderate-low HEI (Q2:  $41.31 \leq \text{DII} < 49.15$ ), moderate-high HEI (Q3:  $49.15 \leq \text{DII} < 58.15$ ), and high HEI (Q4:  $\text{DII} \geq 58.15$ ).

## Infertility

Participants were categorized into two groups based on their responses to the RHQ074 question from the reproductive health questionnaires: “Have you ever attempted to become pregnant for at least a year without success?” Those who answered “Yes” were classified as infertility, while those who answered “No” were classified as fertility.

## Covariant

Our study included the following covariates: age, race, BMI, age at menarche, pelvic inflammatory disease, marital status, education level, smoking, drinking, diabetes, hypertension, and participation in vigorous recreational activities.

## Statistical Analysis

All statistical analyses utilized the recommended weighting method for complex NHANES data (<https://www.cdc.gov/nchs/nhanes/index.htm>). Categorical variables were reported as frequencies and percentages, whereas continuous variables were reported as medians and interquartile ranges (IQR). Pearson’s chi-square test was employed to compare categorical variables between fertility and infertility women. We used multivariate logistic regression to examine the relationship between DII and infertility risk, adjusting for confounders including age, race, BMI, age at menarche, pelvic inflammatory disease, marital status, education level, smoking, alcohol consumption, diabetes, hypertension, and participation in vigorous recreational activities. Nonlinear associations between DII and infertility were assessed using restricted cubic splines (RCS) with three knots at the 10<sup>th</sup>, 50<sup>th</sup>, and 90<sup>th</sup> percentiles. Subgroup analyses were conducted based on age, race, BMI, education level, marital status, smoking, drinking, diabetes, hypertension, pelvic inflammatory disease, and vigorous recreational activities to evaluate heterogeneity among different groups. We also investigated the correlation between DII and HEI using Spearman method and performed multivariate logistic regression including both DII and HEI to explore the association between HEI and infertility risk. Finally, we employed a lasso regression model with 10-fold cross-validation to select predictive variables and developed a nomogram for predicting infertility. All statistical analyses were performed using R software version 4.1.6 (<http://www.r-project.org>), with a two-tailed P-value < 0.05 considered statistically significant.

## Results

### Demographics and Characteristics of Participants

This study included 3184 women of childbearing age, with 12.41% (395/3184) classified as infertility. The baseline characteristics of all participants are detailed in [Table 1](#). The age of the participants was 33.00 (26.00 to 40.00) years, and the DII score was 2.04 (0.94 to 3.00). Compared to women without infertility, those with infertility had higher age, BMI, and DII scores ([Tables 1 and 2](#)). Additionally, women with infertility had higher rates of smoking, hypertension, diabetes, and pelvic inflammatory disease, while they engaged less in vigorous recreational activities ([Table 1](#)). Comparing the components of the DII between the two groups revealed that women with infertility had higher scores for fiber, vitamin A, and vitamin C, whereas differences in other components were not statistically significant ([Table 2](#)).

### Association of Between DII and Infertility

This study further examined the relationship between the DII and the risk of infertility. Initially, when DII was treated as a continuous variable, multivariate logistic regression analysis revealed a positive association between DII and infertility risk in both unadjusted and Model 1 (adjusted for age, race, and BMI) regression models. However, after adjusting for

**Table 1** Demographics and Characteristics of All Participants

Variables	Fertility (N=2789)	Infertility (N=395)	Total (N=3184)	$\chi^2 / H$	P
Age (years)	32.00 (26.00, 39.00)	36.00 (30.00, 41.00)	33.00 (26.00, 40.00)	37.561	<0.001
Age of menarche (years)	12.00 (11.00, 13.00)	12.00 (11.00, 13.00)	12.00 (11.00, 13.00)	0.008	0.929
Body Mass Index (kg/m <sup>2</sup> )	28.20 (23.50, 34.10)	31.30 (24.65, 37.40)	28.50 (23.50, 34.70)	28.191	<0.001
Race, n(%)					
Mexican American	457 (16.4%)	59 (14.9%)	516 (16.2%)	4.264	0.371
Other Hispanic	292 (10.5%)	36 (9.1%)	328 (10.3%)		
Non-Hispanic White	898 (32.2%)	147 (37.2%)	1045 (32.8%)		
Non-Hispanic Black	684 (24.5%)	94 (23.8%)	778 (24.4%)		
Other Race	458 (16.4%)	59 (14.9%)	517 (16.2%)		
Education level, n(%)					
Less than high school	420 (15.1%)	54 (13.7%)	474 (14.9%)	0.531	0.767
High school	532 (19.1%)	76 (19.2%)	608 (19.1%)		
More than high school	1837 (65.9%)	265 (67.1%)	2102 (66%)		
Marital status, n(%)					
Married	1325 (47.5%)	260 (65.8%)	1585 (49.8%)	51.144	<0.001
Single	1250 (44.8%)	104 (26.3%)	1354 (42.5%)		
Living with partner	214 (7.7%)	31 (7.8%)	245 (7.7%)		
Smoking, n(%)					
No	2019 (72.4%)	254 (64.3%)	2273 (71.4%)	10.688	0.001
Yes	770 (27.6%)	141 (35.7%)	911 (28.6%)		
Drinking, n(%)					
No	679 (24.3%)	79 (20%)	758 (23.8%)	3.367	0.067
Yes	2110 (75.7%)	316 (80%)	2426 (76.2%)		
Vigorous activity, n(%)					
No	2257 (80.9%)	317 (80.3%)	2574 (80.8%)	0.062	0.803
Yes	532 (19.1%)	78 (19.7%)	610 (19.2%)		
Moderate activity, n(%)					
No	1615 (57.9%)	235 (59.5%)	1850 (58.1%)	0.296	0.586
Yes	1174 (42.1%)	160 (40.5%)	1334 (41.9%)		
Vigorous recreational activities, n(%)					
No	1921 (68.9%)	300 (75.9%)	2221 (69.8%)	7.870	0.005
Yes	868 (31.1%)	95 (24.1%)	963 (30.2%)		
Moderate recreational activities, n(%)					
No	1488 (53.4%)	217 (54.9%)	1705 (53.5%)	0.288	0.591
Yes	1301 (46.6%)	178 (45.1%)	1479 (46.5%)		
Minutes sedentary activity, n(%)					
<360min	1362 (48.8%)	190 (48.1%)	1552 (48.7%)	0.048	0.827
≥360min	1427 (51.2%)	205 (51.9%)	1632 (51.3%)		

(Continued)

**Table 1** (Continued).

Variables	Fertility (N=2789)	Infertility (N=395)	Total (N=3184)	$\chi^2 / H$	P
Hypertension, n(%)					
No	2377 (85.2%)	313 (79.2%)	2690 (84.5%)	9.011	0.003
Yes	412 (14.8%)	82 (20.8%)	494 (15.5%)		
Diabetes, n(%)					
No	2638 (94.6%)	357 (90.4%)	2995 (94.1%)	15.074	<0.001
Yes	107 (3.8%)	32 (8.1%)	139 (4.4%)		
Borderline	44 (1.6%)	6 (1.5%)	50 (1.6%)		
Pelvic inflammatory disease, n(%)					
No	2667 (95.6%)	359 (90.9%)	3026 (95%)	15.491	<0.001
Yes	122 (4.4%)	36 (9.1%)	158 (5%)		

**Table 2** Comparison of Each Component of DII Scores Between Individuals with Infertility and Individuals Without Infertility

Variables	Fertility (N=2789)	Infertility (N=395)	Total (N=3184)	H	P
DII	1.99 (0.92, 2.97)	2.27 (1.09, 3.14)	2.04 (0.94, 3.00)	5.824	0.016
Alcohol	0.28 (0.28, 0.28)	0.28 (0.28, 0.28)	0.28 (0.28, 0.28)	0.244	0.621
$\beta$ -Carotene	0.51 (0.22, 0.55)	0.52 (0.32, 0.55)	0.51 (0.23, 0.55)	3.295	0.069
Caffeine	0.08 (0.08, 0.08)	0.08 (0.08, 0.08)	0.08 (0.08, 0.08)	3.247	0.072
Carbohydrate	-0.06 (-0.09, -0.00)	-0.07 (-0.09, 0.00)	-0.06 (-0.09, -0.00)	0.221	0.639
Cholesterol	-0.03 (-0.11, 0.01)	-0.03 (-0.11, 0.01)	-0.03 (-0.11, 0.01)	0.217	0.641
Energy	-0.07 (-0.16, 0.03)	-0.06 (-0.15, 0.02)	-0.07 (-0.16, 0.02)	0.088	0.767
Fiber	0.38 (-0.01, 0.60)	0.48 (0.05, 0.62)	0.39 (-0.00, 0.60)	11.508	<0.001
Folic acid	0.18 (0.10, 0.19)	0.18 (0.09, 0.19)	0.18 (0.10, 0.19)	0.080	0.777
Iron	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.01)	1.911	0.167
Magnesium	0.16 (-0.02, 0.28)	0.18 (0.01, 0.31)	0.16 (-0.01, 0.29)	3.472	0.062
Monounsaturated fatty acids	0.00 (-0.00, 0.01)	0.00 (-0.00, 0.01)	0.00 (-0.00, 0.01)	0.483	0.487
Niacin	0.08 (-0.01, 0.15)	0.07 (-0.02, 0.14)	0.08 (-0.01, 0.15)	0.509	0.476
N3 fatty acids	-0.13 (-0.25, 0.00)	-0.13 (-0.27, 0.00)	-0.13 (-0.25, 0.00)	0.100	0.752
N6 fatty acids	0.12 (0.12, 0.13)	0.12 (0.12, 0.13)	0.12 (0.12, 0.13)	0.170	0.68
Protein	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)	0.289	0.591
Polyunsaturated fatty acids	-0.04 (-0.23, 0.12)	-0.04 (-0.25, 0.11)	-0.04 (-0.23, 0.12)	0.270	0.603
Selenium	-0.10 (-0.17, -0.01)	-0.10 (-0.16, -0.01)	-0.10 (-0.17, -0.01)	0.593	0.441
Saturated fat	-0.18 (-0.32, 0.01)	-0.16 (-0.31, 0.01)	-0.18 (-0.32, 0.01)	0.113	0.737
Total fat	-0.02 (-0.19, 0.12)	0.00 (-0.18, 0.12)	-0.02 (-0.18, 0.12)	0.266	0.606
Zinc	0.08 (-0.06, 0.25)	0.07 (-0.04, 0.24)	0.08 (-0.05, 0.25)	0.017	0.897
Vitamin A	0.26 (0.15, 0.33)	0.28 (0.18, 0.33)	0.27 (0.16, 0.33)	6.581	0.010
Vitamin B1	0.04 (-0.00, 0.07)	0.04 (0.01, 0.07)	0.04 (-0.00, 0.07)	0.464	0.496
Vitamin B2	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.03)	0.803	0.370
Vitamin B6	-0.04 (-0.18, 0.11)	-0.04 (-0.16, 0.11)	-0.04 (-0.17, 0.11)	0.256	0.613
Vitamin B12	-0.05 (-0.08, -0.00)	-0.05 (-0.07, -0.00)	-0.05 (-0.08, -0.00)	0.411	0.522
Vitamin C	0.31 (0.04, 0.41)	0.37 (0.11, 0.41)	0.32 (0.05, 0.41)	11.737	<0.001
Vitamin D	0.44 (0.44, 0.44)	0.44 (0.44, 0.44)	0.44 (0.44, 0.44)	1.609	0.205
Vitamin E	0.16 (-0.03, 0.40)	0.23 (-0.01, 0.40)	0.18 (-0.03, 0.40)	0.971	0.324

additional confounders—including age of menarche, pelvic inflammatory disease, marital status, education level, smoking, alcohol consumption, diabetes, hypertension, and vigorous recreational activities—in Model 2, the association between DII and infertility risk was no longer significant ( $p > 0.05$ ) (Table 3). Similarly, when DII was categorized, no

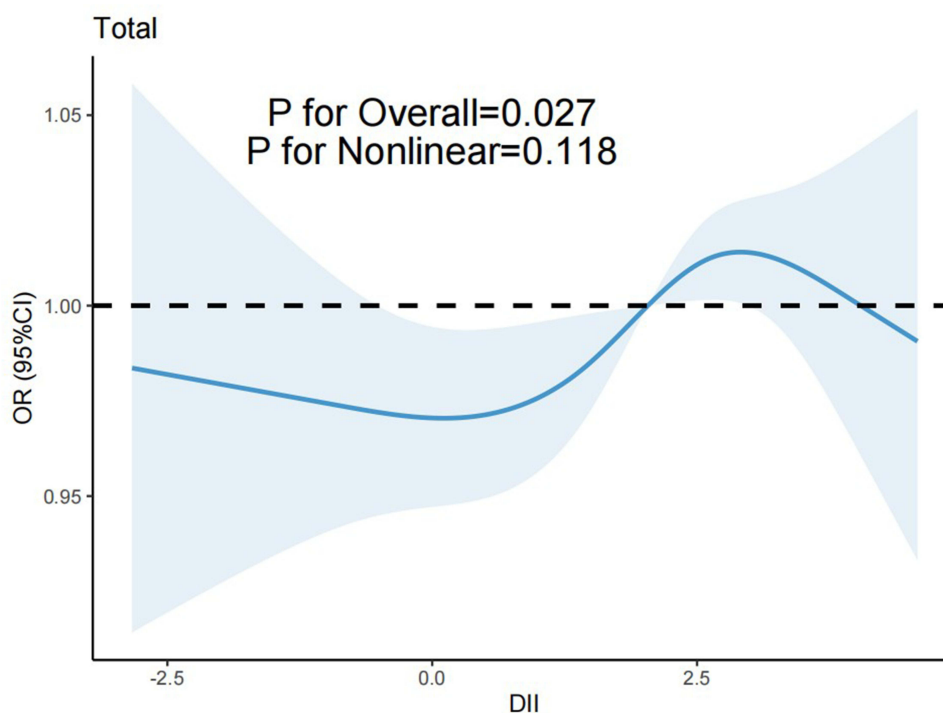
**Table 3** Logistic Regression Analysis on the Association Between DII and Infertility Risk

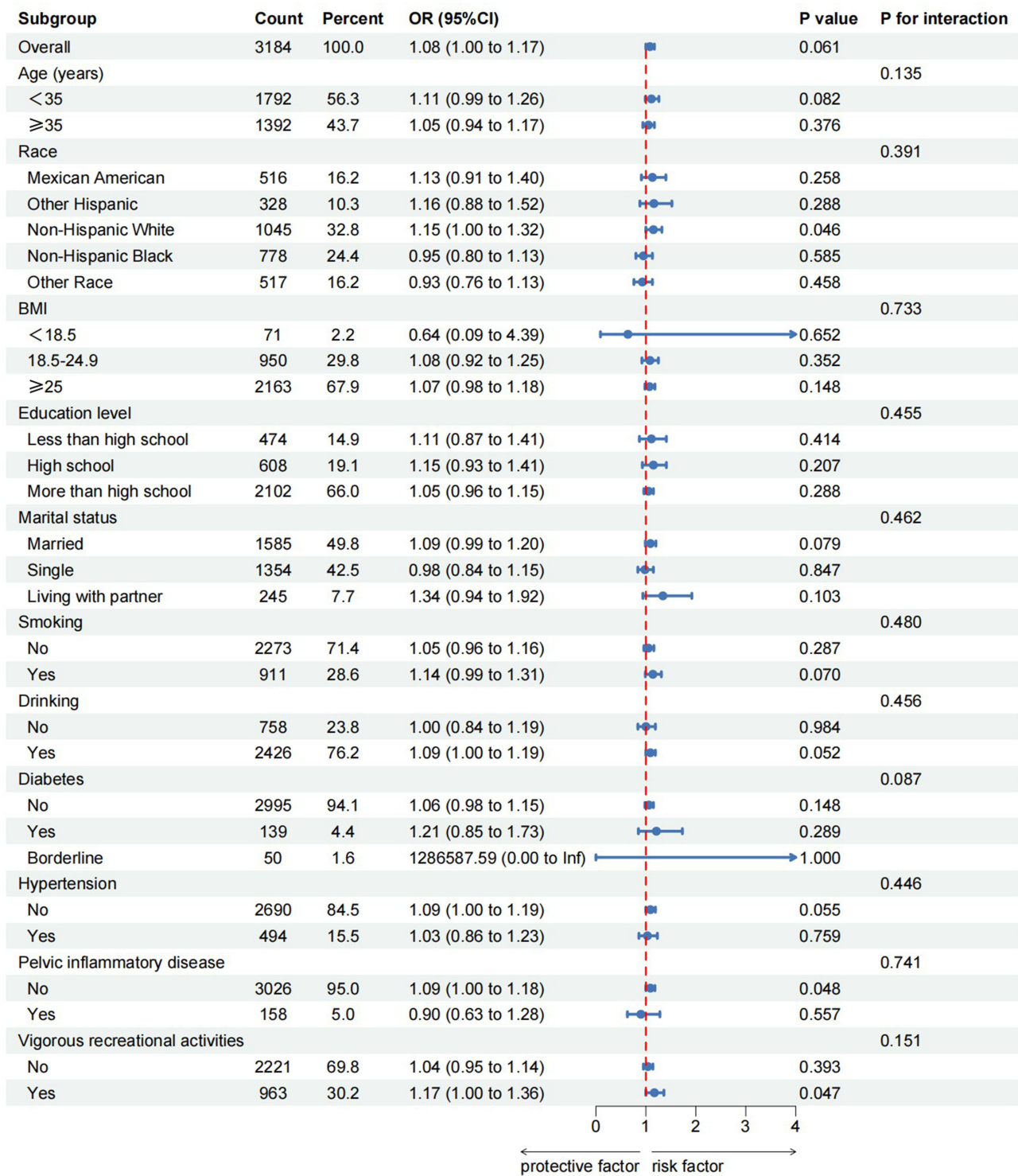
	Nonadjusted Model		Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
DII	1.09 (1.01–1.17)	0.024	1.09 (1.01–1.17)	0.031	1.08 (1.00–1.17)	0.061
DII(Quartile)						
Q1	Reference	-	Reference	-	Reference	-
Q2	0.89 (0.65–1.22)	0.467	0.89 (0.65–1.23)	0.487	0.88 (0.63–1.21)	0.426
Q3	1.24 (0.92–1.68)	0.150	1.25 (0.92–1.69)	0.155	1.22 (0.89–1.66)	0.214
Q4	1.32 (0.99–1.78)	0.062	1.31 (0.97–1.78)	0.076	1.28 (0.94–1.76)	0.123

**Notes:** Data are presented as OR (95% CI). Nonadjusted Model: No covariates were adjusted. Model 1: Age, race, and BMI were adjusted. Model 2: Age, race, BMI, age of menarche, pelvic inflammatory disease, marital status, education levels, smoking, drinking, diabetes, hypertension, and vigorous recreational activities were adjusted.

**Abbreviations:** OR, odds ratio; CI, confidence interval; BMI, body mass index; DII, Dietary Inflammation Index; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

significant relationship with infertility risk was observed (all  $p > 0.05$ ) (Table 3). Furthermore, RCS analysis indicated no non-linear relationship between DII and infertility risk ( $p$  for non-linearity = 0.118) (Figure 2). Finally, subgroup analyses were conducted to explore the relationship between DII and infertility across different populations. Figure 3 shows that none of the stratifying variables—including age (<35 years and  $\geq 35$  years), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race), BMI (<18.5, 18.5–24.9, and  $\geq 25$ ), education level (Less than high school, High school, and More than high school), marital status (Married, Single, and Living with partner), smoking (yes and no), alcohol consumption (yes and no), diabetes (yes and no), hypertension (yes and no), pelvic inflammatory disease (yes and no), and vigorous recreational activities (yes and no)—had a significant impact on the relationship between DII and infertility (all  $p$  for interaction  $> 0.05$ ).

**Figure 2** The RCS analysis on the association between DII and infertility risk.

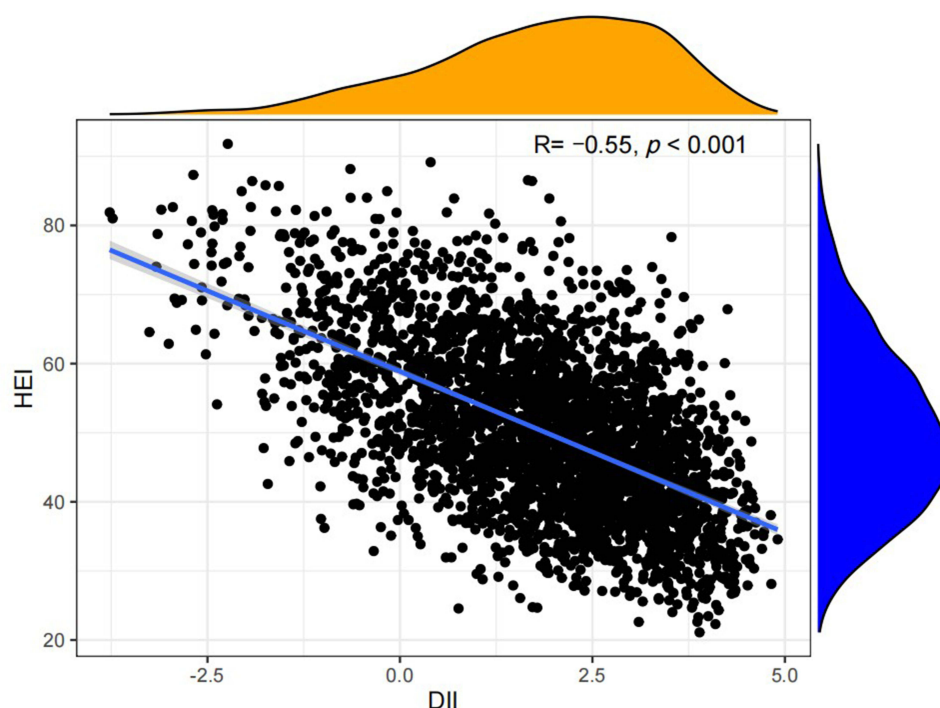


**Figure 3** Subgroup analysis of the association of the DII and infertility risk. Each stratification was adjusted for age, race, BMI, age of menarche, pelvic inflammatory disease, marital status, education levels, smoking, drinking, diabetes, hypertension, and vigorous recreational activities.

**Abbreviations:** OR, odds ratio; BMI, body mass index; DII, Dietary Inflammation Index; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; Inf, Infinity.

## Association of the DII Scores and the HEI Scores in Infertility Females

We also calculated another dietary index, the HEI scores, commonly used to assess diet quality. Initially, we examined the correlation between DII and HEI among all participants, as shown in [Figure 4](#). A significant negative correlation was



**Figure 4** The association between the DII scores and the HEI scores in infertile females. The yellow and blue curves in the scatter plot represent the marginal distributions of the variables DII and HEI, respectively.

**Abbreviations:** DII, Dietary Inflammation Index; HEI, Health Eating Index.

found between DII and HEI ( $R = -0.55$ ;  $p < 0.001$ ). We then compared HEI scores and their components between the two groups. The total fruits score was significantly lower in women with infertility compared to those without infertility ( $p < 0.05$ ), while no significant differences were observed for HEI scores and other components between the two groups (Table 4). Based on these findings, DII may be a better predictor of infertility.

## Development of a Nomogram Model for Predicting Infertility Risk

Compared to HEI, DII is a more effective predictor of infertility. Therefore, we used 10-fold cross-validation with Lasso regression to identify key infertility-related factors among eight covariates (age, BMI, marital status, smoking, hypertension, diabetes, vigorous recreational activities, and pelvic inflammatory disease) and 28 dietary components of the DII scores. Lasso regression revealed age, BMI, marital status, diabetes, pelvic inflammatory disease, and seven key dietary factors (alcohol,  $\beta$ -Carotene, fiber, niacin, polyunsaturated fatty acids, vitamin A, and vitamin C) as significant predictors for the final nomogram (Figure 5). The ROC curve analysis demonstrated the nomogram model's predictive performance with an AUC of 85.1% (95% CI: 74.7%–95.5%) (Figure 6).

## Discussion

This paper investigates the association between two dietary indicators, the DII and the HEI, and the risk of infertility using data from the nationally representative NHANES (2013–2020). The study found that women of reproductive age with infertility had significantly higher DII scores (2.27 [1.09, 3.14]) compared to those without infertility (1.99 [0.92, 2.97]), indicating that a pro-inflammatory diet may increase the risk of infertility. In contrast, there was no significant difference in HEI scores between the two groups (47.78 [40.17 to 56.57] vs 49.26 [41.42 to 58.38]). These results suggest that dietary modifications, particularly increasing the intake of anti-inflammatory diets, could improve female fertility and reduce the risk of infertility.

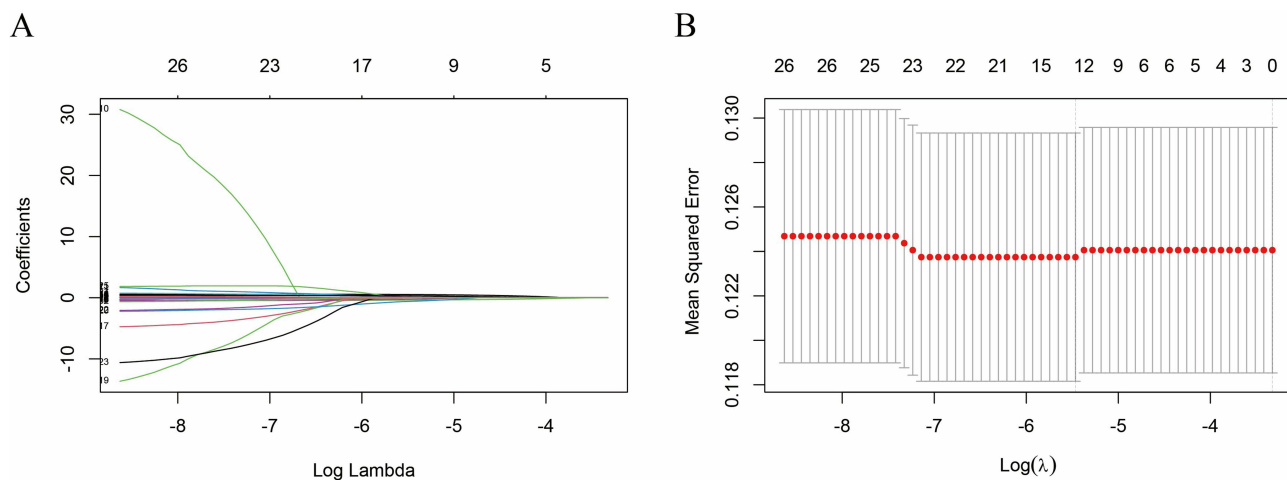
Poor dietary habits have long been recognized as significant contributors to infertility. Previous research has explored the link between various dietary patterns and infertility. The Western diet, characterized by high consumption of simple

**Table 4** Comparison of Each Component of HEI Scores Between Individuals with Infertility and Individuals Without Infertility

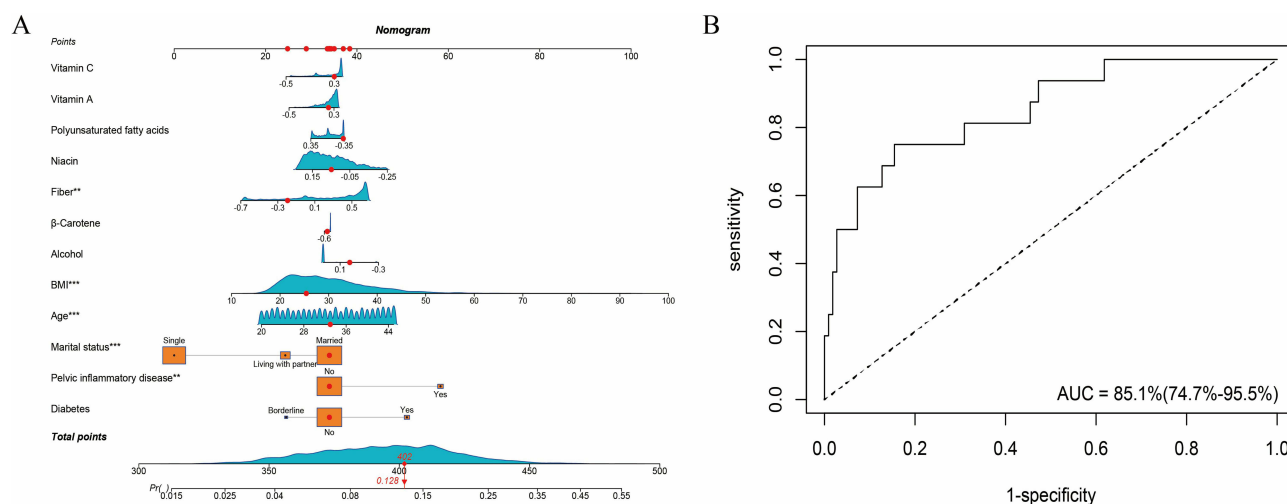
Variables	Fertility (N=2789)	Infertility (N=395)	Total (N=3184)	H	P
HEI	49.26 (41.42 to 58.38)	47.78 (40.17 to 56.57)	49.15 (41.31 to 58.16)	3.547	0.06
Total Fruits	2.06 (0.16 to 3.50)	1.33 (0.08 to 2.91)	1.99 (0.15 to 3.41)	9.901	0.002
Whole Fruits	2.38 (0.00 to 3.49)	1.29 (0.00 to 2.84)	2.27 (0.00 to 3.36)	3.328	0.068
Total Vegetables	3.06 (2.01 to 4.13)	3.01 (1.89 to 3.98)	3.05 (2.00 to 4.10)	2.472	0.116
Greens and Beans	1.66 (0.00 to 2.50)	1.10 (0.00 to 2.50)	1.62 (0.00 to 2.50)	2.623	0.105
Total Protein Foods	4.53 (3.55 to 5.00)	4.67 (3.62 to 5.00)	4.55 (3.57 to 5.00)	2.039	0.153
Seafood and Plant Proteins	2.50 (0.36 to 3.56)	2.50 (0.05 to 3.67)	2.50 (0.33 to 3.60)	0.167	0.683
Whole Grains	1.27 (0.00 to 4.05)	0.95 (0.00 to 3.82)	1.25 (0.00 to 4.04)	1.284	0.257
Dairy	4.75 (2.67 to 6.70)	4.64 (2.62 to 6.56)	4.74 (2.65 to 6.67)	0.860	0.354
Fatty Acids	5.15 (3.08 to 7.34)	5.12 (2.98 to 7.16)	5.15 (3.06 to 7.33)	0.100	0.752
Refined Grains	5.61 (3.80 to 8.27)	6.12 (3.89 to 8.38)	5.68 (3.81 to 8.29)	1.294	0.255
Sodium	4.24 (2.12 to 6.22)	4.06 (2.25 to 6.16)	4.21 (2.14 to 6.22)	0.132	0.717
Added Sugars	7.43 (4.93 to 9.29)	7.07 (4.46 to 9.21)	7.37 (4.86 to 9.28)	2.295	0.13
Saturated Fats	6.11 (4.07 to 8.23)	5.96 (3.99 to 7.91)	6.08 (4.06 to 8.21)	0.740	0.39

carbohydrates (mainly from sugar, sweets, and sugar-sweetened beverages), red meat, and processed meats, combined with low intake of fresh fruits, vegetables, whole grains, poultry, and fish, constitutes a high glycemic index diet rich in saturated and trans fatty acids. This dietary pattern significantly increases the risk of anovulatory infertility in women through its detrimental effects on endocrine metabolism and ovarian reserve.<sup>18,19</sup>

In contrast, anti-inflammatory dietary patterns, such as the Mediterranean diet, the Healthy Nordic Diet, and the Okinawan Diet, have been associated with reduced inflammation and a potentially protective effect against infertility. Key components of these anti-inflammatory diets include monounsaturated fats, flavonoids, vitamins C and E, and polyphenols, which are prevalent in plant foods, berries, fish, and whole grains. These components are known to reduce inflammation and have been linked to improved fertility outcomes.<sup>20–22</sup> A nested case-control study of Spanish university graduates found that women with high adherence to the Mediterranean diet—characterized by elevated consumption of fruits, vegetables, fish, poultry, low-fat products, and olive oil—experienced a significant increase in fertility. This diet reduces the risk of weight gain and insulin resistance (IR), potentially increasing the likelihood of pregnancy. Insulin



**Figure 5** The LASSO penalized regression analysis for identifying key infertility-related factors. **(A)** The coefficient shrinkage process of eight covariates (age, BMI, marital status, smoking, hypertension, diabetes, vigorous recreational activities, and pelvic inflammatory disease) and 28 dietary components of the DII scores. Each different color line represents the trajectory of a distinct coefficient as the regularization parameter  $\lambda$  changes. **(B)** A LASSO-based ordinal logistic model with 10-fold cross-validation based on the minimal mean squared error (MSE) was employed to find the optimal parameter ( $\lambda$ ).  
**Abbreviations:** LASSO, least absolute shrinkage and selection operator.



**Figure 6** Establishment and validation of a prediction nomogram model to predict infertility risk. **(A)** A nomogram model incorporating age, BMI, marital status, diabetes, pelvic inflammatory disease, and seven key dietary factors (alcohol, β-Carotene, fiber, niacin, polysaturated fatty acids, vitamin A, and vitamin C as determined by LASSO regression analysis. \*\* P value < 0.01; \*\*\* P value < 0.001. **(B)** ROC curve assessing the predictive accuracy for infertility risk.

**Abbreviations:** LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic.

resistance can adversely affect ovarian function and may contribute to infertility by inducing oxidative stress, disrupting energy metabolism, impairing oocyte development and embryo quality, affecting endometrial receptivity, and interfering with hormone secretion and embryo implantation.<sup>4,23,24</sup> Extensive evidence from observational and interventional studies indicates an inverse relationship between plant-based dietary patterns, including the Mediterranean diet, and oxidative stress and pro-inflammatory biomarkers. Plant-based diets with anti-inflammatory effects, following the Mediterranean pattern, appear to positively influence fertility.<sup>4</sup>

Dysregulation of either the degree or duration of inflammatory events is strongly associated with the pathophysiology of infertility. There is growing evidence suggesting that various infertility-related diseases are linked with chronic low-grade inflammation.<sup>25</sup> While inflammation is a normal bodily response to infection, irritation, or injury, a prolonged state of low-grade inflammation can adversely affect fertility. Research has demonstrated that inflammation impacts nearly the entire reproductive process, including the ovaries, uterus, embryo, and implantation.<sup>26</sup> Diets high in DII lead to elevated levels of inflammatory markers such as CRP and interleukins. These elevated levels have the potential to interfere with ovarian hormone production, impede egg maturation and release, and affect endometrial angiogenesis and cell proliferation. As a result, this reduced endometrial tolerance may hinder successful embryo implantation.<sup>27,28</sup> Moreover, inflammation and oxidative stress can damage the meiotic and cytoplasmic maturation processes of oocytes, thereby diminishing their developmental capacity for fertilization and preimplantation embryo development. Conversely, a low DII diet can help support reproductive health by reducing oxidative stress and fighting free radicals.<sup>20</sup> Several reproductive conditions associated with infertility, such as polycystic ovary syndrome (PCOS) and endometriosis, are also linked to chronic inflammation. Patients with these conditions often exhibit elevated levels of inflammatory markers. Excessive and persistent inflammatory stimulation can induce oxidative stress and fibrosis in the ovaries, leading to reduced oocyte quality, impaired ovulation, or ovarian rupture, ultimately resulting in infertility.<sup>5,29–33</sup>

Our study found a positive association between the DII and infertility risk, consistent with prior research. For example, Jie Qi et al analyzed data from NHANES (2013–2018) involving 3496 women and discovered that higher DII scores were positively correlated with infertility among participants aged 18–45 years. Additionally, anti-inflammatory diets were suggested to potentially improve infertility outcomes.<sup>14</sup> Similarly, a recent study examining diet and female fertility found that diets with higher inflammatory potential were associated with a greater likelihood of self-reported lifetime infertility, whereas adherence to low-inflammatory diets and

Mediterranean-style eating patterns was linked to a lower incidence of lifetime infertility.<sup>34</sup> In our study, we also employed the HEI to assess diet quality and found that DII and HEI exhibited a negative correlation. However, no relationship between HEI and infertility was observed, indicating that DII was a more effective predictor of infertility compared to HEI. Previous studies have demonstrated an association between HEI and DII, where higher HEI scores (reflecting better adherence to the Dietary Guidelines for Americans (DGA)) were associated with lower DII scores (indicating a stronger anti-inflammatory diet). Compared to HEI, DII provides insights into a different aspect of dietary variability related to inflammation, offering additional valuable information beyond other commonly used dietary indices. DII captures specific dietary aspects (ie, inflammatory potential) directly related to the development of many chronic diseases.<sup>12,13</sup>

In addition to these key findings, our study developed a nomogram prediction model for assessing infertility risk using 10-fold cross-validation with LASSO regression. Twelve predictor variables were identified through this analysis, including vitamin C, vitamin A, niacin, fiber, beta-carotene, polyunsaturated fatty acids, alcohol, BMI, age, marital status, pelvic inflammatory disease, and diabetes mellitus. The model demonstrated strong performance, as evidenced by column-line graph plots and ROC curve analysis. While previous studies have developed predictive models for low fertility populations with relatively low discriminatory power (AUC: 59–64%), another study that included couples with varied fertility potential developed a pregnancy prediction model incorporating socio-demographic factors, lifestyle and behavioral factors, and dietary quality, achieving good predictive performance.<sup>35,36</sup> In contrast, our study, which focuses on dietary aspects influencing infertility risk in women of childbearing age, presents a model with high predictive efficacy. This approach may offer deeper insights into various prediction methods and assist in the prediction and management of infertility in clinical settings.

Our study offers several strengths and has important implications. One of its primary strengths is the use of a weighted, representative population with a substantial sample size. However, the study also has limitations. As a cross-sectional study, it cannot establish causality, and further prospective research is needed. Additionally, DII and HEI calculations are based on 24-hour dietary recalls. While this is the standard method for dietary assessment, it may be subject to recall bias, as participants may not be able to accurately report all food and beverage intakes from the preceding 24 hours. Furthermore, a single day's dietary status may not fully represent an individual's long-term eating habits and could introduce potential biases. Infertility is a multifactorial condition influenced by genetics and a range of lifestyle factors, with significant variation across ethnic groups. Despite including numerous relevant covariates in our model, we faced challenges in completely addressing the effects of unmeasured or residual confounders. Another limitation of this paper is that the proportion of positive samples for the target variable is relatively low. Specifically, the infertility rate in the study was only 12.41% (395 out of 3184). This imbalance in the data distribution may cause the prediction model to favor predicting the majority class. As a result, the model's ability to identify the minority class (eg, the high-risk group for infertility) is reduced. Nonetheless, the predictive power has been maximized by employing cross-validation methods, with AUC values exceeding 85%. While our study demonstrates that a pro-inflammatory diet is associated with an increased risk of infertility among American women, generalizing these findings to Asian populations requires further investigation. Therefore, additional research is needed to validate and expand upon our results. Future studies should aim to more comprehensively analyze the complex pathophysiological mechanisms underlying infertility and further explore the impact of residual risk factors. Such research will contribute to developing new strategies for the treatment and prevention of infertility.

## Conclusion

This study reveals a significant association between pro-inflammatory diets, as reflected in the DII diet score, and the risk of infertility in American women of reproductive age, suggesting that dietary adjustments can be an effective strategy for preventing infertility. Therefore, developing relevant policy interventions, promoting anti-inflammatory dietary concepts, and integrating nutrition and reproductive health education into public health programs warrant further investigation. Furthermore, to translate these findings into clinical practice, future research

should prioritize longitudinal studies to establish causal relationships, validate the applicability of the DII model in different populations, and evaluate the actual effectiveness of anti-inflammatory dietary interventions in improving fertility through randomized controlled trials.

## Data Sharing Statement

The original research data for this study was sourced from NHANES, which can be accessed and downloaded from the official website (<https://www.cdc.gov/nchs/nhanes/>).

## Ethics Approval and Consent to Participate

The Institutional Review Board of the National Center for Health Statistics reviewed and approved the project (<https://www.cdc.gov/nchs/nhanes/irba98.htm>), and written informed consent was obtained from all participants. The survey followed the ethical guidelines set forth in the Declaration of Helsinki. The Ethics Committee of Longyan First Affiliated Hospital of Fujian Medical University waived the necessity of ethical approval for this study, as the NHANES is a publicly accessible database.

## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

## Author Contributions

Xiaoli Dong: methodology, writing—original draft, writing—review and editing, funding acquisition, formal analysis and data curation. Fang Xie: writing—review and editing and formal analysis. Ping Li: Conceptualization, resources, supervision, project administration, writing—review & editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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## Disclosure

The authors declare no conflicts of interest.

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