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Development and predictive value of the empirical dietary inflammatory index for pregnant women in the second trimester

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ABSTRACT: Background: We aim to develop and validate the empirical dietary inflammatory index for pregnant women in the second trimester (EDII-PW) and assess its predictive value for maternal and neonatal outcomes. **Methods:** We utilized data from three sub-cohorts conducted in Hefei, China, including the Maternal and Infant Health Cohort (MIH-I: 2015-2019) with 5,052 pregnant women, MIH-II (2018-2022) with 1,932 pregnant women, and MIH-III (2023-2024) with 1,225 pregnant women, all recruited between gestational ages of 16 and 23 weeks. The development and validation of the EDII-PW index were based on three plasma inflammatory biomarkers (IL-6, hsCRP, and TNF-α) in MIH-I. In MIH-II, three additional biomarkers (E-selectin, VCAM-1, and ICAM-1) were included for independent biomarker validation. In MIH-III, six biomarkers (hsCRP, IL-6, TNF-α, E-selectin, VCAM-1, and ICAM-1) were measured in 1,225 participants and were used to derive inflammatory and endothelial biomarker profiles for the outcome prediction analyses. **Results:** The EDII-PW was significantly associated with plasma concentrations of inflammatory biomarkers. In MIH-I, participants in the highest quartile of EDII-PW had significantly higher levels of hsCRP, IL-6, and TNF-α compared to those in the lowest quartile. Similar associations were observed for E-selectin, VCAM-1, and ICAM-1 in MIH-II. In MIH-III, ROC curve analyses suggested that multivariable models containing the EDII-PW may discriminate maternal and neonatal outcomes, with AUC values as follows: 0.81 for premature rupture of membranes (PROM), 0.83 for gestational diabetes mellitus (GDM), 0.74 for endothelial dysfunction, 0.81 for inflammatory status, 0.80 for low birth weight (LBW), 0.82 for small for gestational age (SGA), 0.83 for preterm birth, and 0.76 for gestational hypertension. **Conclusion:** The EDII-PW showed reproducible associations with inflammatory biomarkers across independent sub-cohorts and potential utility as a component of multivariable models for adverse maternal and neonatal outcomes.

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1. Introduction

Dietary patterns are key determinants of health[1]. During pregnancy, maternal diet significantly influences maternal health and fetal development, particularly during the second trimester[2]. A meta-analysis showed that suboptimal dietary patterns during pregnancy are linked to gestational diabetes, hypertension, preterm birth, low birth weight, and other negative birth outcomes[3]. For example, another systematic review demonstrated an association between a pro-inflammatory diet during pregnancy and increased risks of preterm birth and low birth weight, mediated by elevated inflammation[4]. Conversely, adhering to a healthy dietary pattern rich in vegetables, fruits, whole grains, nuts, legumes, fish, and plant oils may reduce inflammation and lower the risk of metabolic syndrome[5]. Although dietary patterns are linked to inflammation in the general population, specific tools to assess dietary inflammatory potential in pregnant women are lacking. Furthermore, existing longitudinal studies often have limited sample sizes. Given that the inflammatory state varies across gestational trimesters, this study specifically focused on the second trimester.

There are two main approaches to deriving dietary patterns: the a priori (index-based) method and the a posteriori (data-driven) method. Recently, the integration of a posteriori empirical evidence with advanced statistical methods has been recognized as an effective approach for developing hypothesis-driven dietary patterns[6]. For example, using data from a health screening center in China, a dietary pattern derived with C-reactive protein as the response variable was linked to an increased risk of metabolic syndrome in a dose-response manner[7]. Another study developed a dietary index for hyperinsulinemia, derived using inflammatory biomarkers and C-peptide as response variables, which was significantly positively associated with the risk of developing type 2 diabetes[8]. However, most dietary patterns developed using inflammatory markers as response variables suffer from limitations such as small sample sizes, cross-sectional study designs, and a focus on single inflammatory biomarkers. Therefore, it is essential to create dietary inflammatory indices through large-scale longitudinal studies that include various inflammatory biomarkers.

Studies predicting adverse pregnancy outcomes have examined glycolipid metabolism indicators[9], circulating exosomal hsa_circRNA[10], and transcriptomic biomarkers[11,12]. However, when considering time and economic costs, dietary indicators offer the advantage of convenience and efficiency compared to exploring biological indicators and genetic structures. A meta-analysis of six observational studies consistently found that higher dietary inflammatory index scores were positively associated with an increased risk of overweight, obesity, metabolic disorders, and elevated levels of inflammatory biomarkers in adolescents[13]. Another meta-analysis, including nine prospective studies, found that populations with greater dietary inflammatory potential had significantly higher risks of all-cause mortality, cardiovascular disease-related mortality, cancer-related mortality, and cardiovascular disease incidence[14]. However, there is a lack of research evaluating the predictive value of the empirical dietary inflammatory index for maternal and neonatal health outcomes in pregnant women. In summary, using data from MIH-Hefei's three sub-cohorts,

we aim to: 1) Construct the dietary inflammatory index for pregnant women (EDII-PW) in the second trimester; 2) Validate it using three inflammatory and three endothelial biomarkers in an independent cohort; and 3) Predict maternal and neonatal outcomes in a third cohort.

2. Methods

2.1 Setting and Design

The Maternal and Infant Health (MIH) cohorts in Hefei, China, were established to investigate the effects of environmental exposures, lifestyle factors, nutritional monitoring, and genetic determinants on pregnancy complications and birth outcomes (MIH-I), offspring neurodevelopment (MIH-II), and metabolism (MIH-III). Specifically, MIH-I was primarily designed to develop dietary indices and their association with inflammatory biomarkers. MIH-II focused on validating these indices using additional endothelial biomarkers. MIH-III was prospectively designed to assess the predictive value of these indices for clinically ascertained maternal and neonatal outcomes. Individuals were recruited from three centers: Anhui Women and Child Health Care Hospital, the First People's Hospital of Hefei City, and the First Affiliated Hospital of Anhui Medical University. Recruitment for the MIH-I cohort took place between March 2015 and October 2019, while recruitment for MIH-II occurred between June 2018 and December 2022. Recruitment for MIH-III was conducted from January 2023 to February 2024. These centers constitute 70% of the city's prenatal outpatient volume.

2.2 Participants

The inclusion criteria were a gestational age between 16 and 23 weeks, no communication barriers, natural conception, delivery at a designated hospital, and singleton pregnancy. Exclusion criteria included multiple pregnancies, inability to provide informed consent, lack of blood samples, incomplete demographic data during pregnancy, and inadequate or incomplete dietary data, and hs-CRP levels ≥10 mg/L (indicating potential acute inflammation)[15]. In MIH-I, 6,111 individuals were recruited, with 5,052 included after exclusions. For MIH-II, 2,405 were recruited, with 1,932 included. In MIH-III, 1,897 were recruited, with 1,225 included (Supplemental Fig.1). We gathered detailed information on demographics, medical history, lifestyle factors, dietary habits, environmental exposures, and other confounding factors through standardized face-to-face questionnaires and the hospital's electronic system. To develop the EDII-PW, we calculated the average daily intake of 40 food groups from the FFQ in MIH-I. In MIH-III, maternal and neonatal outcomes were collected for all 1,225 included participants, all participants also had available measurements of the six inflammatory and endothelial biomarkers used for the subsequent latent profile and ROC analyses. The study adhered to relevant guidelines and regulations, and all participants provided written informed consent. The study received approval from the Ethics Committee (No. 2015002).

2.3 Assessment of biomarkers

In MIH-I, hsCRP, IL-6, and TNF-α were measured in 5,052 eligible plasma samples. In MIH-II and MIH-III, all six biomarkers were measured in 1,932 and 1,225 participants, respectively. Blood samples were

collected at 16–23 weeks of gestation after an overnight fast (≥8 hours) into EDTA-containing tubes. Samples were centrifuged at 900 × g for 15 min, and plasma aliquots were stored at −80°C until analysis. hsCRP was measured using a DiaSorin chemiluminescent immunoassay (Liaison® XL, DiaSorin, Saluggia, Italy). IL-6 and TNF-α were quantified using R&D Systems ELISA kits (catalogue Nos. D6050 and DTA00D, respectively). E-selectin, VCAM-1, and ICAM-1 were measured using Huamei Biotech ELISA kits (Wuhan, China; catalogue Nos. E051h, E056h, and E062h, respectively). The same assay manufacturers, catalogue numbers, and harmonized laboratory protocols were used in MIH-II and MIH-III; samples from the cohorts were assayed in separate batches because of their different recruitment periods.

The detection limits were 0.1 mg/L for hsCRP, 0.1 pg/mL for IL-6, 0.2 pg/mL for TNF-α, 0.1 ng/mL for E-selectin and ICAM-1, and 0.2 ng/mL for VCAM-1. In MIH-I, the intra-assay CVs for hsCRP, IL-6, and TNF-α were 4.8%, 5.2%, and 4.5%, respectively, and the corresponding inter-assay CVs were 7.5%, 8.9%, and 7.2%. In MIH-II, the intra-assay CVs for these three markers were 5.1%, 5.8%, and 4.7%, respectively. For E-selectin, VCAM-1, and ICAM-1, the intra-assay CVs were 6.3%, 5.9%, and 6.1%, respectively, and the inter-assay CVs were 9.2%, 8.7%, and 9.5%, respectively. All available intra-assay CVs were below 10%, and all available inter-assay CVs were below 15%. Pooled plasma quality-control samples were included in each assay run, and 5% blanks and 5% duplicate samples were included in each batch.

2.4 Dietary Assessment

The dietary instrument used in this study was a culturally adapted, semi-quantitative FFQ covering approximately 40 food groups commonly consumed by pregnant women in Hefei, China. The questionnaire was administered by trained interviewers during gestational weeks 16-23 and assessed usual dietary intake over the preceding month. Before implementation in the MIH cohort, the FFQ underwent instrument-specific reliability and validity evaluation among 400 pregnant women at 16-23 weeks of gestation from the target population. Relative validity was assessed by comparing food-group intake estimated from the FFQ with intake obtained from repeated 24-hour dietary recalls. Reproducibility was evaluated using a test-retest design, and the internal consistency and construct validity of the questionnaire were also examined (Supplemental Table 1). The FFQ collected information on consumption frequency and usual portion size. Portions were recorded using natural units (e.g., one cup of milk, one egg, or one apple) or standard weight and volume measures. Consumption frequency was converted to daily frequency using prespecified factors: never (0 times/day), 1-2 times/week (0.2/day), 3-6 times/week (0.6/day), and at least once/day (1/day).

2.5 Confounding variables

Confounding variables were collected through standardized face-to-face interviews and extracted from the hospital electronic information system. These variables included age (years) and pre-pregnancy body mass index (BMI), which was calculated as weight divided by height squared (kg/m²), physical activity (using the International Physical Activity Questionnaire (IPAQ)[16], categorizing participants into three groups: <3, 3-6, ≥6days/week, at least 30 minutes per session), household income (<8000, ≥8000,

yuan/month, according to the classification criteria in the Hefei City Yearbook), maternal education (<13years, ≥13years, "<13 years" indicates educational attainment at the level of high school or below, "≥13 years" implies educational attainment at the level of college or above); gestational weight gain (kg); parity (1, ≥2); passive smoking (exposed to secondhand cigarette smoking during pregnancy, yes or no); alcohol drinking (any alcoholic beverages 3 months before or during pregnancy; yes/no); total energy intake (kcal/day); chronic diseases (diabetes, hypertension, heart disease, or rheumatoid arthritis; yes/no); family history of diabetes (yes/no); and family history of hypertension (yes/no).

2.6 Development of the EDII-PW

We calculated the average daily intake of 40 food groups collected through the FFQ in MIH-I during the second trimester. Then, we applied Reduced Rank Regression (RRR) to identify dietary patterns associated with the inflammatory markers IL-6, hsCRP, and TNF-α. The first factor obtained from RRR, referred to as the RRR dietary pattern, was retained for further analysis. Next, we used stepwise linear regression analysis to identify significant food groups influencing the RRR dietary pattern. A significance level of $P < 0.05$ was used for entering and retaining variables in the model. The identified food groups were weighted by their regression coefficients from the final model and summed to form the EDII score. To facilitate interpretation, the EDII was divided by 1000 to reduce the magnitude of the scores. The EDII-PW assesses the inflammatory potential of the diet, with higher scores indicating greater inflammatory potential and lower scores indicating lower inflammatory potential. The three response biomarkers were selected a priori to capture complementary components of maternal systemic inflammation. hsCRP represents a relatively stable downstream acute-phase response, whereas IL-6 and TNF-α are key upstream pro-inflammatory cytokines involved in immune activation and metabolic inflammation. These biomarkers have been widely used in studies of dietary inflammatory potential. However, they were not intended to comprehensively represent the entire maternal or placental inflammatory network. Accordingly, the EDII-PW should be interpreted as an empirical dietary index associated with selected circulating markers of maternal systemic inflammation during the second trimester.

2.7 Maternal and neonatal outcomes

In MIH-III, we collected data on maternal and neonatal outcomes from 1,225 individuals. All the individuals underwent a routine 2-hour 75-gram oral glucose tolerance test (OGTT) between the 24th and 28th weeks of gestation. The criteria for diagnosing gestational diabetes mellitus (GDM) were based on the guidelines of the International Association of Diabetes in Pregnancy Study Groups, as endorsed by the American Diabetes Association[17]. GDM was diagnosed if at least one of the plasma glucose concentrations was abnormal: fasting ≥5.1 mmol/L, 1-hour ≥10 mmol/L, or 2-hour ≥8.5 mmol/L after the 75-gram OGTT; The collected pregnancy outcome data included gestational age and gestational hypertension, defined as the onset of high blood pressure after 20 weeks of pregnancy, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and no proteinuria[18]; LBW is defined as birth weight <2500 g, regardless of gestational age[19]; SGA as birth weight <10th percentile, adjusted for gestational age and sex[20]; Preterm

birth was defined as delivery before 37 completed weeks of gestation[21]; Inflammatory status was based on hsCRP, IL-6, and TNF-α, whereas endothelial dysfunction was based on E-selectin, VCAM-1, and ICAM-1. Both outcomes were classified using latent profile analysis (LPA), as described in the statistical analysis section; PROM was defined as rupture of the fetal membranes prior to the onset of labor, irrespective of gestational age, with documented amniotic fluid leakage[22].

2.8 Statistical analysis

Participant characteristics were summarized using means ± SDs for continuous variables, geometric means ± CVs for log-transformed variables, and frequencies (%) for categorical variables. All six biomarkers were log-transformed before analysis to normalize distributions and converted back to original units for reporting to enhance clinical interpretability. Spearman's correlation coefficients assessed relationships between EDII-PW and biomarkers. To develop the EDII-PW, we calculated the average daily intake of 40 food groups from the FFQ in MIH-I. We opted for a whole-food approach to capture dietary patterns as consumed, reflecting real-world eating behaviors and facilitating practical dietary recommendations. We applied Reduced Rank Regression (RRR) to identify dietary patterns associated with IL-6, hsCRP, and TNF-α, retaining the first factor. Stepwise linear regression ($P < 0.05$) identified significant food groups, which were weighted by their coefficients and summed to form the EDII-PW, then divided by 1000 for interpretability. The EDII-PW assesses dietary inflammatory potential, with higher scores indicating greater pro-inflammatory effects. For the ROC analysis of EDII-PW, latent profile analysis was utilized to convert the three inflammatory markers and three endothelial markers into binary variables[23]. For the ROC analyses in MIH-III, latent profile analysis (LPA) was performed separately using the three inflammatory biomarkers (hsCRP, IL-6, and TNF-α) and the three endothelial biomarkers (E-selectin, VCAM-1, and ICAM-1) measured in all 1,225 participants. Models with two to five latent classes were evaluated using the Akaike information criterion (AIC), Bayesian information criterion (BIC), entropy, Lo-Mendell-Rubin likelihood ratio test (LMR-LRT), class proportions, clinical interpretability, and model stability. Although AIC and BIC decreased as the number of classes increased, the two-class solution was selected for both biomarker sets because it showed the highest entropy (0.947 for inflammatory biomarkers and 0.944 for endothelial biomarkers), contained no small classes (<5% of the sample), yielded clinically interpretable subgroups, and showed the best overall stability. The two resulting classes were subsequently used as binary outcomes representing inflammatory status and endothelial dysfunction in the ROC analyses (Supplemental Tables 8 and 9). The adjusted ROC curves were constructed using predicted probabilities derived from multivariable logistic regression models. Each model included the EDII-PW as the primary predictor and was adjusted for age, pre-pregnancy BMI, physical activity, household income, maternal education, gestational weight gain, parity, passive smoking, total energy intake, family history of diabetes, and chronic diseases. Outcome-specific complete-case analysis was prespecified. However, no data were missing for the corresponding outcomes, EDII-PW, or covariates in MIH-III; therefore, all outcome-specific models included 1,225 participants, as reported in Supplemental Table 10. Multiple imputation was not performed. All AUCs

were calculated using the pROC package in R version 4.1.3, and comparisons between models were performed using the DeLong test. The association between the EDII-PW and biomarkers was evaluated using multivariable-adjusted linear regression models. This approach calculated the relative concentrations of biomarkers across quartiles, using the lowest quartile (Q1) as the reference. All other analyses were conducted using R version 4.1.3 and SPSS version 21.0 (IBM Corp., Armonk, NY, USA). A two-tailed P value < 0.05 was considered statistically significant.

To assess the robustness of models with fewer than 10 events per predictor parameter, sensitivity analyses were conducted for gestational hypertension, premature rupture of membranes, preterm birth, and low birth weight using ridge-penalized logistic regression. The same 13 prespecified predictor parameters used in the primary models were retained, and the penalty parameter was selected by cross-validation. Internal validation was performed using 1,000 bootstrap resamples. For each outcome, the apparent AUC from the original model and the optimism-corrected AUC, calibration slope, and Brier score from the ridge-penalized analysis were reported. Bootstrap optimism was estimated as the mean difference between performance in each bootstrap sample and performance when the bootstrap-fitted model was applied to the original sample.

2.9 Sensitivity analysis

We created three alternative versions of the EDII-PW to assess robustness. (1) Unweighted EDII: all 19 food groups from Table 1 were assigned equal absolute weights (+1 for pro-inflammatory, –1 for anti-inflammatory) instead of regression coefficients. (2) Nutrient-based EDII: daily intakes of vitamins C, D, and E from foods were estimated by multiplying the reported consumption frequency and portion size of each food by its nutrient content in the China Food Composition Tables [24]. For vitamin supplements, information on brand, dose, and frequency of use was collected during the interview and incorporated into the estimated daily intake. These nutrient estimates were entered as additional candidate variables in the RRR and stepwise-regression procedure. (3) BMI-adjusted EDII: the stepwise linear regression model was additionally adjusted for pre-pregnancy BMI (continuous, kg/m²).

Table 1. Components of the EDII-PW and Spearman correlation coefficients with biomarkers in MIH-I (n = 5,052, 2015-2019).

	RRR dietary pattern	EDII	hsCRP	IL-6	TNF-α	Weights[a]
RRR dietary pattern b	1.00	0.95	0.35	0.29	0.25	NA
EDII-PW		1.00	0.34	0.31	0.29	NA
Positive associations						
Desserts	0.25	0.19	0.21	0.20	0.11	317.3
Processed meat	0.18	0.17	0.19	0.16	0.12	175.3
High-energy drinks	0.16	0.12	0.15	0.14	0.10	182.6
Pickled vegetables	0.17	0.16	0.12	0.11	0.10	121.1
Fried foods	0.21	0.19	0.17	0.16	0.13	208.7
Snacks	0.12	0.16	0.14	0.14	0.11	178.5
Red meats	0.28	0.15	0.12	0.11	0.10	162.4
Organ meats	0.25	0.16	0.13	0.12	0.11	55.2
Condiments	0.19	0.14	0.11	0.10	0.09	103.9
Inverse associations						
Tea	-0.38	-0.19	-0.17	-0.16	-0.14	-145.6

	RRR dietary pattern	EDII	hsCRP	IL-6	TNF-α	Weights[a]
Bean products	-0.49	-0.22	-0.20	-0.20	-0.17	-102.1
Nuts	-0.23	-0.24	-0.23	-0.21	-0.18	-154.8
Vegetable oil	-0.21	-0.11	-0.09	-0.07	-0.06	-78.4
Fruits	-0.36	-0.19	-0.16	-0.15	-0.11	-94.0
Fish, shrimp and shellfish	-0.17	-0.22	-0.18	-0.19	-0.16	-221.6
Eggs	-0.27	-0.38	-0.28	-0.26	-0.21	-118.9
Whole grains	-0.19	-0.31	-0.27	-0.23	-0.17	-342.1
White meats	-0.14	-0.29	-0.21	-0.18	-0.20	-92.3
Vegetables	-0.37	-0.22	-0.18	-0.11	-0.09	-242.3

[a] regression coefficients for each EDII-PW component obtained from the last step of the stepwise linear regression analysis. [b] RRR dietary pattern was the first factor obtained from RRR with all food groups. It was then retained for subsequent analyses as the dependent variable in the stepwise linear regression analyses to identify the most important food groups contributing to this pattern. Abbreviation: hsCRP, high-sensitivity C-reactive protein; EDII-PW, empirical dietary inflammatory index for pregnant women; NA, not applicable; RRR, reduced rank regression; IL-6, Interleukin-6; TNF-α, tumor necrosis factor Alpha.

3. Results

The associations between each food group and biomarkers are detailed in Supplemental Table 2 within the RRR model. The stepwise linear regression model identified 19 food groups as significant contributors to the EDII-PW, as presented in Table 1. All dietary data and biomarkers were collected during the second trimester. Food groups such as desserts, processed meats, high-energy drinks, pickled vegetables, fried foods, snacks, red meats, organ meats, and condiments were positively associated with biomarkers. In contrast, tea, bean products, nuts, vegetable oil, fruits, fish, shrimp and shellfish, eggs, whole grains, white meats, and vegetables were inversely associated with biomarkers.

As shown in Table 2, participant characteristics across EDII-PW quartiles varied among the three sub-cohorts. In MIH-I, higher EDII-PW quartiles were generally associated with higher pre-pregnancy BMI, lower household income and educational attainment, greater gestational weight gain and total energy intake, and a higher prevalence of chronic diseases. Concentrations of hsCRP, IL-6, and TNF-α also increased significantly across EDII-PW quartiles. In MIH-II, significant trends were observed for pre-pregnancy BMI, household income, maternal education, gestational weight gain, passive smoking, total energy intake, hsCRP, IL-6, and ICAM-1, whereas several other characteristics and biomarkers did not show significant trends. In MIH-III, significant trends were observed for age, pre-pregnancy BMI, physical activity, household income, maternal education, gestational weight gain, parity, passive smoking, total energy intake, hsCRP, IL-6, and ICAM-1, whereas TNF-α, E-selectin, and VCAM-1 did not show significant trends. Overall, the patterns across EDII-PW quartiles were not entirely consistent among the three sub-cohorts.

Table 2. Participant characteristics across quartiles of the empirical dietary inflammatory index in three sub-cohorts.

Characteristic	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
	MIH-Hefei-I (n=5,052; 2015–2019)				
Quartile cut-offs	Q1 (≤−1.15)	Q2 (−1.15, −1.08)	Q3 (−1.08, 1.96)	Q4 (≥1.97)	
Age, years	32.3 (4.5)	32.6 (3.9)	33.1 (4.2)	32.7 (4.3)	0.001
Pre-pregnancy BMI, kg/m²	21.34 (2.80)	21.4 (2.91)	22.53 (3.01)	23.72 (3.02)	<0.001
Physical activity <3 days/week, n (%)	655 (51.9)	662 (52.4)	690 (54.6)	710 (56.2)	0.015

Characteristic	Q1	Q2	Q3	Q4	*P* for trend
Household income <8,000 yuan/month, n (%)	837 (66.3)	839 (66.4)	884 (70.0)	895 (70.9)	0.003
Maternal education <13 years, n (%)	422 (33.4)	448 (35.5)	499 (39.5)	538 (42.6)	<0.001
Gestational weight gain, kg	7.0 (4.2)	7.1 (4.5)	7.3 (4.2)	7.5 (4.9)	0.002
Parity ≥2, n (%)	582 (46.1)	586 (46.4)	590 (46.7)	625 (49.5)	0.094
Passive smoking, n (%)	505 (40.0)	509 (40.3)	528 (41.8)	543 (43.0)	0.089
Alcohol consumption, n (%)	1 (0.08)	3 (0.24)	5 (0.40)	6 (0.48)	0.049
Total energy, kcal/day	1954 (541)	1759.4 (513.1)	1978.0 (559)	2011 (568.2)	<0.001
Family history of diabetes, n (%)	91 (7.2)	104 (8.2)	93 (7.4)	124 (9.8)	0.043
Chronic diseases, n (%)	122 (9.7)	138 (10.9)	163 (12.9)	169 (13.4)	0.001
hsCRP, mg/L	3.22 (1.21)	3.83 (2.31)	4.14 (2.82)	4.53 (3.21)	<0.001
IL-6, pg/mL	132.41 (115.02)	196.71 (151.72)	197.62 (181.71)	211.08 (151.04)	<0.001
TNF-α, pg/mL	53.81 (33.52)	59.08 (42.40)	60.82 (46.33)	62.64 (45.52)	<0.001
MIH-Hefei-II (n=1,932; 2018–2022)					
Quartile cut-offs	Q1 (≤−1.73)	Q2 (−1.73, −1.11)	Q3 (−1.11, 2.13)	Q4 (≥2.14)	
Age, years	33.9 (4.4)	34.1 (4.2)	33.9 (4.2)	34.2 (4.3)	0.421
Pre-pregnancy BMI, kg/m²	21.57 (2.99)	21.85 (3.10)	21.94 (3.12)	22.06 (3.18)	0.013
Physical activity <3 days/week, n (%)	235 (48.7)	236 (48.9)	258 (53.5)	259 (53.6)	0.056
Household income <8,000 yuan/month, n (%)	254 (52.6)	258 (53.4)	275 (56.9)	299 (61.9)	0.002
Maternal education <13 years, n (%)	141 (29.2)	178 (36.9)	182 (37.7)	224 (46.4)	<0.001
Gestational weight gain, kg	6.7 (4.5)	6.8 (4.6)	7.1 (4.8)	7.3 (5.1)	0.030
Parity ≥2, n (%)	265 (54.9)	271 (56.1)	278 (57.6)	292 (60.5)	0.070
Passive smoking, n (%)	167 (34.6)	181 (37.5)	208 (43.1)	222 (46.0)	<0.001
Alcohol consumption, n (%)	1 (0.21)	2 (0.41)	4 (0.83)	4 (0.83)	0.137
Total energy, kcal/day	1631 (538)	1918.5 (489.2)	2023 (540)	2178.5 (577.1)	<0.001
Family history of diabetes, n (%)	45 (9.3)	46 (9.5)	43 (8.9)	48 (9.9)	0.834
Chronic diseases, n (%)	45 (9.3)	39 (8.1)	51 (10.6)	59 (12.2)	0.068
hsCRP, mg/L	3.62 (3.29)	3.84 (3.34)	4.10 (3.92)	4.46 (5.89)	0.001
IL-6, pg/mL	164.71 (122.66)	202.57 (207.94)	207.22 (187.19)	225.13 (137.26)	<0.001
TNF-α, pg/mL	57.52 (41.72)	59.71 (45.25)	60.52 (42.56)	62.33 (46.98)	0.090
E-selectin, ng/mL, median (IQR)	5.68 (3.63, 8.10)	5.87 (3.70, 9.06)	5.94 (3.60, 9.10)	6.01 (3.57, 9.15)	0.180
VCAM-1, ng/mL, median (IQR)	91.94 (67.02, 120.15)	93.93 (69.04, 146.43)	95.17 (68.06, 147.92)	96.40 (67.07, 149.41)	0.191
ICAM-1, ng/mL, median (IQR)	255.81 (201.34, 310.17)	266.12 (207.83, 356.78)	269.39 (208.17, 346.34)	272.66 (208.51, 335.90)	0.007
MIH-Hefei-III (n=1,225; 2023–2024)					
Quartile cut-offs	Q1 (≤−1.64)	Q2 (−1.64, −1.28)	Q3 (−1.28, 2.96)	Q4 (≥2.97)	
Age, years	33.9 (4.0)	34.3 (4.1)	34.5 (4.2)	34.7 (4.4)	0.015
Pre-pregnancy BMI, kg/m²	21.21 (2.80)	21.66 (2.89)	21.89 (2.98)	22.11 (3.07)	<0.001
Physical activity <3 days/week, n (%)	141 (46.1)	149 (48.7)	157 (51.3)	165 (53.7)	0.045
Household income <8,000 yuan/month, n (%)	141 (46.1)	148 (48.4)	160 (52.3)	172 (56.0)	0.008
Maternal education <13 years, n (%)	109 (35.6)	114 (37.3)	123 (40.2)	132 (43.0)	0.044
Gestational weight gain, kg	6.0 (4.1)	6.4 (4.3)	7.1 (4.6)	7.9 (4.9)	<0.001
Parity ≥2, n (%)	168 (54.9)	177 (57.8)	184 (60.1)	192 (62.5)	0.045
Passive smoking, n (%)	150 (49.0)	155 (50.7)	166 (54.2)	177 (57.7)	0.021
Alcohol consumption, n (%)	0	0	1 (0.33)	1 (0.33)	0.206
Total energy, kcal/day	1850 (540)	1964.1 (561.3)	2077 (575)	2190 (588.2)	<0.001

Characteristic	Q1	Q2	Q3	Q4	*P* for trend
Family history of diabetes, n (%)	24 (7.8)	27 (8.8)	29 (9.5)	32 (10.4)	0.254
Chronic diseases, n (%)	27 (8.8)	23 (7.5)	29 (9.5)	35 (11.4)	0.128
hsCRP, mg/L	3.65 (3.25)	3.88 (3.38)	4.15 (3.95)	4.50 (5.92)	0.003
IL-6, pg/mL	166.5 (124.0)	204.8 (210.0)	209.5 (189.0)	227.5 (138.5)	0.002
TNF-α, pg/mL	58.1 (42.1)	60.3 (45.7)	61.2 (43.0)	63.0 (47.4)	0.072
E-selectin, ng/mL, median (IQR)	5.72 (3.65, 8.15)	5.91 (3.72, 9.10)	5.98 (3.62, 9.12)	6.05 (3.59, 9.18)	0.130
VCAM-1, ng/mL, median (IQR)	92.5 (67.5, 121.0)	94.5 (69.5, 147.0)	95.8 (68.5, 148.5)	97.0 (67.5, 150.0)	0.217
ICAM-1, ng/mL, median (IQR)	257.5 (202.5, 312.0)	268.0 (209.0, 358.0)	271.0 (209.5, 348.0)	274.5 (210.0, 337.5)	0.004

The three alternative EDII versions—unweighted EDII, nutrient-based EDII, and BMI-adjusted EDII—are detailed in Supplemental Table 3. EDII-PW and its three alternative versions demonstrated low to moderate correlations (r = 0.09-0.39) with hsCRP, IL-6, and TNF-α in both cohorts (Supplemental Table 4). They exhibited low to moderate correlations (r = 0.12-0.31) with E-selectin, VCAM-1, and ICAM-1 in MIH-II. As shown in Table 3, significant associations between the EDII-PW and the relative concentrations of biomarkers were observed in MIH-I after adjusting for multiple variables. For hsCRP, the relative concentration for Q4 compared to Q1 was 2.63 (95% CI: 1.19, 4.06). For IL-6, the relative concentration for Q4 compared to Q1 was 1.94 (95% CI: 1.65, 2.24). For TNF-α, the relative concentration for Q4 compared to Q1 was 1.62 (95% CI: 1.34, 1.84). Additionally, tests for linear trend indicated significant findings for each biomarker across quartiles of the EDII-PW.

Table 3. Relative concentrations (95% CIs) of inflammatory biomarkers across quartiles of the EDII-PW in MIH-Hefei-I (2015–2019).

Models[a]	EDII-PW				
	Q1 (N= 1,263)	Q2 (N= 1,263)	Q3 (N= 1,263)	Q4 (N= 1,263)	*P* for trend
hsCRP					
Unadjusted	Ref.	3.63 (1.65, 5.61)	4.97 (1.83, 8.10)	5.53 (4.81, 6.25)	<0.001
Multivariable-adjusted	Ref.	1.41 (1.12, 1.59)	2.32 (1.43, 3.21)	2.63 (1.19, 4.06)	<0.001
IL-6					
Unadjusted	Ref.	2.37 (2.02, 2.72)	3.35 (1.99, 4.71)	4.31 (1.46, 7.17)	<0.001
Multivariable-adjusted	Ref.	1.31 (1.23, 1.38)	1.82 (1.41, 2.22)	1.94 (1.65, 2.24)	<0.001
TNF-α					
Unadjusted	Ref.	1.60 (1.16, 2.04)	2.24 (1.61, 2.88)	2.74 (2.39, 3.11)	<0.001
Multivariable-adjusted	Ref.	1.17 (1.09, 1.26)	1.41 (1.16, 1.74)	1.62 (1.34, 1.84)	<0.001

[a] The unadjusted model does not account for confounding variables. The multivariable-adjusted model is based on linear regression adjusted for confounding variables of age, pre-pregnancy BMI, physical activity, household income, maternal education, gestational weight gain, parity, passive smoking, total energy, family history of diabetes and chronic disease.

During the validation phase in MIH-II, the EDII-PW demonstrated significant associations not only with the biomarkers hsCRP, IL-6, and TNF-α, but also with three additional biomarkers: E-selectin, VCAM-1, and ICAM-1. Significant linear trends in the concentrations of all biomarkers across the quartiles of EDII-PW were observed (Figure 1 and Supplemental Table 5). For instance, for hsCRP, the relative concentrations (95% CIs) comparing the highest to the lowest quartile of EDII-PW were 2.63 (95% CI:1.17, 4.19), for IL-6 were 2.35 (95% CI: 1.92, 2.78), and for TNF-α were 1.66 (95% CI: 1.11, 2.21). Similar trends were observed

for the other three biomarkers, E-selectin, VCAM-1, and ICAM-1. For E-selectin, the relative concentrations (95% CIs) comparing the highest to the lowest quartile of EDII-PW were 3.34 (2.56, 4.12), and for VCAM-1 and ICAM-1, they were 2.61 (1.88, 3.34) and 1.75 (1.53, 1.97), respectively. For sensitivity analysis, we examined the associations of the three alternative EDII versions with biomarkers in both cohorts. In the development phase (MIH-I), associations with hsCRP, IL-6, and TNF-α are shown in Supplemental Table 6, with Panels A, B, and C presenting results for the unweighted EDII, nutrient-based EDII, and BMI-adjusted EDII, respectively. In the validation phase (MIH-II), associations with all six biomarkers are shown in Supplemental Table 7, using the same panel structure. In both cohorts, all three alternative versions showed significant associations with the biomarkers, albeit with lower magnitudes compared to the original EDII-PW.

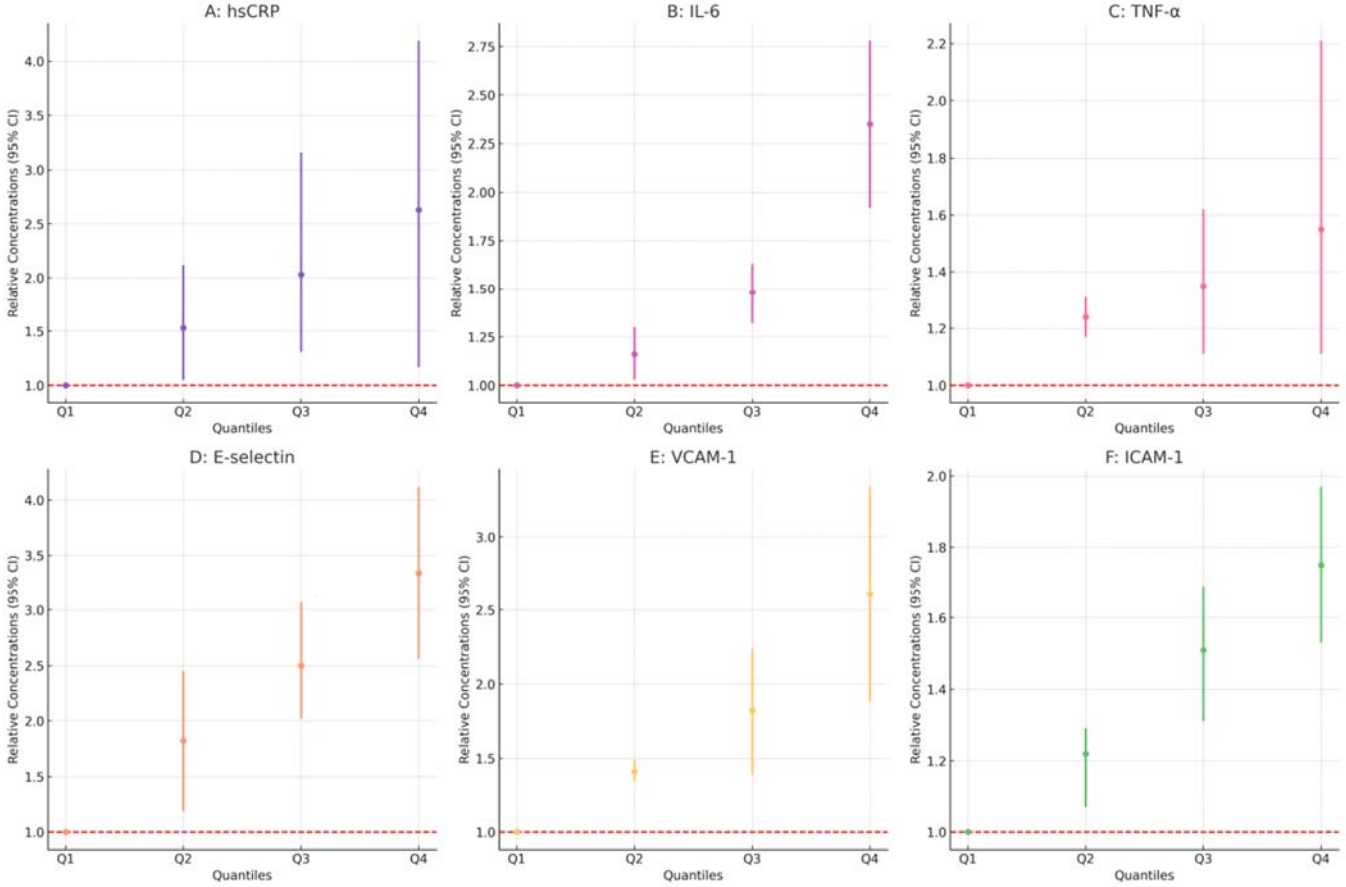


Fig. 1 Relative concentrations (with 95% CIs) of biomarkers across quartiles of the EDII-PW in MIH-II (n= 1,932, 2018-2022).
The model was constructed using linear regression analysis, adjusting for potential confounders including age, pre-pregnancy BMI, physical activity, household income, maternal education, gestational weight gain, parity, passive smoking, total energy intake, and family history of diabetes and chronic disease.
Abbreviations: hsCRP, high-sensitivity C-reactive protein, IL-6, interleukin-6, TNF-α, tumor necrosis factor-alpha, E-selectin, VCAM-1, vascular cell adhesion molecule-1, ICAM-1, intercellular adhesion molecule-1.

In MIH-III, all 1,225 participants had available measurements of the three inflammatory biomarkers (hsCRP, IL-6, and TNF-α) and the three endothelial biomarkers (E-selectin, VCAM-1, and ICAM-1). LPA identified two biomarker profiles for both the inflammatory and endothelial marker sets. The selected two-class models had entropy values of 0.947 and 0.944 for the inflammatory and endothelial profiles, respectively; the smaller classes comprised 551 participants (45.0%) and 601 participants (49.1%), respectively (Supplemental Tables 8 and 9). These classes were subsequently used as binary outcomes

representing inflammatory status and endothelial dysfunction in the ROC analyses. ROC curve analyses were then performed to evaluate the predictive performance of the EDII-PW and its three alternative versions for maternal and neonatal outcomes. The AUCs were 0.81 (95% CI, 0.76-0.87) for PROM, 0.83 (95% CI, 0.75-0.89) for GDM, 0.74 (95% CI, 0.68-0.82) for endothelial dysfunction, 0.81 (95% CI, 0.77–0.85) for inflammatory status, 0.80 (95% CI, 0.74–0.86) for low birth weight, 0.82 (95% CI, 0.75-0.89) for small for gestational age, 0.83 (95% CI, 0.77-0.88) for preterm birth, and 0.76 (95% CI, 0.72-0.82) for gestational hypertension.

After adjustment for potential confounding factors, the AUCs of the multivariable models containing the EDII-PW were above 0.70, indicating acceptable to good discriminatory performance of the complete multivariable models containing the EDII-PW (Figure 2). Across the outcomes, the original EDII-PW generally yielded higher AUCs than the alternative EDII specifications (Figure 2).

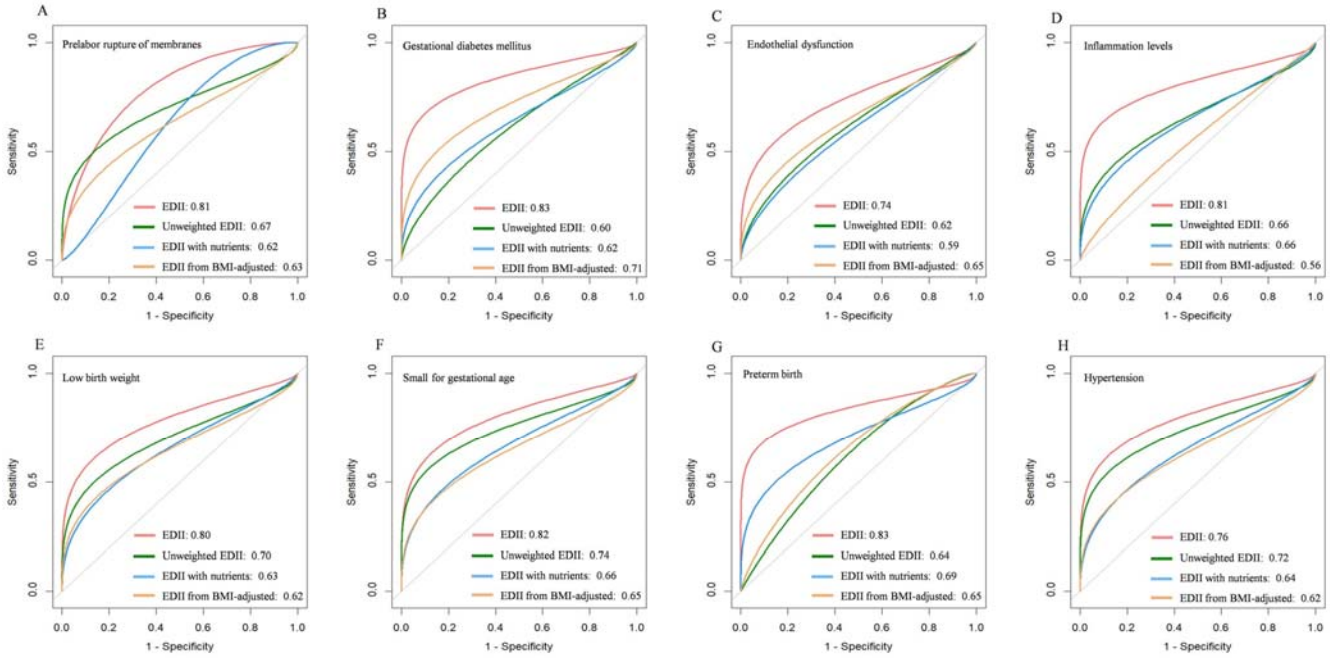


Fig.2 ROC curves and AUCs for multivariable models containing the EDII-PW and its three alternative versions in predicting maternal and neonatal outcomes in MIH-III (n=1,225, 2023-2024).

The adjusted ROC curves were constructed using participant-specific predicted probabilities obtained from separate multivariable logistic regression models. Each model included one dietary inflammatory index and the same prespecified covariates.

In sensitivity analyses of the four outcomes with EPV values below 10, the apparent AUCs from the original models were 0.76 for gestational hypertension, 0.81 for PROM, 0.83 for preterm birth, and 0.80 for low birth weight. Following ridge penalization and bootstrap internal validation, the corresponding optimism-corrected AUCs were 0.73, 0.78, 0.79, and 0.74, respectively. Calibration slopes were 0.93, 0.92, 0.91, and 0.88, and Brier scores were 0.066, 0.058, 0.050, and 0.034, respectively (Supplemental Table 11). The optimism-corrected AUCs remained above 0.70 after ridge penalization and bootstrap correction; however, the attenuation was greatest for low birth weight, supporting cautious and exploratory interpretation of that model.

4. Discussion

For the first time, we developed the EDII-PW specifically for the second trimester of pregnancy and evaluated its associations with biomarkers and its discriminatory performance in multivariable models across three sub-cohorts. In MIH-I, the EDII-PW was developed using three biomarkers: hsCRP, IL-6, and TNF-α. In MIH-II, the independent biomarker validation was expanded to include three additional biomarkers: E-selectin, VCAM-1, and ICAM-1. In MIH-III, multivariable models containing the EDII-PW showed discriminatory performance for maternal and neonatal outcomes. These findings suggest that the EDII-PW may be useful for studying dietary inflammatory potential and its associations with maternal and neonatal health outcomes.

The index, developed based on 19 food groups, addresses a gap in dietary inflammation research specifically for pregnant women. Previously, researchers developed a dietary inflammatory index through a comprehensive literature review and weighted fitting method in a cohort study. Its validation phase was limited to a single inflammatory biomarker[25]. Additionally, several hypothesis-driven dietary indices have been developed; however, these are primarily targeted at postmenopausal women or focus solely on two inflammatory markers. For example, an index developed and validated within a cohort of the Nurses' Health Study demonstrated significant associations with endometrial cancer[26]. Similar approaches have been applied in other populations. In patients undergoing hemodialysis, RRR with CRP and IL-6 as response variables was used to derive inflammation-related dietary patterns, and the CRP-derived pattern was associated with cognitive impairment[27]. In older Taiwanese adults, RRR with CRP and HbA1c as response variables identified dietary patterns associated with lower levels of these biomarkers[28]. Developing hypothesis-driven dietary patterns based on specific disease mechanisms, such as inflammation, could enhance study comparability and clarify biological pathways linking dietary patterns to disease progression[29]. Our study found significant associations between EDII-PW and six biomarkers and evaluated the discriminatory performance of multivariable models containing the EDII-PW for maternal and neonatal outcomes. For sensitivity analyses, we developed three alternative versions of the EDII-PW, all of which showed significant associations with biomarkers, albeit generally weaker than those of the original EDII-PW.

Our study found that higher EDII-PW scores were associated with higher concentrations of three inflammatory and three endothelial biomarkers. Several studies have reported associations between diet and inflammatory markers. In the AUSMED Heart Trial, improvement in dietary inflammatory index score after a 6-month dietary intervention was associated with a reduction in IL-6 among patients with coronary heart disease[30]. In a randomized, double-blind trial among older adults with mild cognitive impairment, food anthocyanin supplementation reduced TNF-α concentrations[31]. These findings are consistent with the biological plausibility of diet-related differences in inflammatory markers. Diets high in saturated fats, trans fats, and refined sugars have been shown to increase the production of pro-inflammatory cytokines such as IL-6 and TNF-α[32]. These cytokines can trigger a cascade of inflammatory reactions that exacerbate insulin resistance, leading to metabolic disorders like GDM[33]. Conversely, anti-inflammatory diets rich in omega-3

fatty acids, antioxidants, and polyphenols, commonly found in fruits, vegetables, nuts, and fish, can reduce inflammatory markers[34]. These dietary components inhibit the production of pro-inflammatory cytokines and promote the secretion of anti-inflammatory cytokines, thus mitigating inflammatory responses[35]. The EDII-PW captures dietary inflammatory potential and may contribute to multivariable risk assessment. Although the evaluated maternal and neonatal outcomes have distinct etiologies, several partially overlapping biological pathways may link a pro-inflammatory dietary pattern to multiple pregnancy complications. Maternal systemic inflammation may interact with insulin resistance and glucose dysregulation in GDM, endothelial activation and impaired vascular adaptation in gestational hypertension, placental perfusion and fetal growth in SGA and LBW, and extracellular-matrix degradation and membrane weakening in PROM and preterm birth. Nevertheless, these shared pathways do not establish outcome-specific causality, and each complication is also influenced by genetic, infectious, obstetric, placental, and environmental determinants. The EDII-PW should therefore be regarded as a nonspecific dietary-exposure indicator that may contribute to multivariable risk assessment, rather than as a stand-alone diagnostic tool for any individual pregnancy complication.

The AUC values for the multivariable models predicting maternal and neonatal outcomes were all above 0.70, indicating potential discriminatory utility. Previous prospective studies have reported associations between dietary inflammatory indices and the risks of type 2 diabetes[36] and gestational diabetes[25]. A cohort study from Australia found that a traditional vegetable dietary pattern significantly reduced the risk of preterm birth, particularly among nulliparous women[37]. A meta-analysis found an association between the Asian diet quality index and cardiovascular disease risk[38]. These studies are consistent with the possibility that dietary patterns may be associated with maternal and neonatal health outcomes. Additionally, research has shown that healthy dietary patterns, such as those rich in fruits, vegetables, and whole grains, can significantly reduce the risk of pregnancy complications[39]. Another study found that a Mediterranean diet, which includes a high intake of vegetables, fruits, olive oil, and whole grains, can lower the risk of adverse pregnancy outcomes in mainly White populations[40]. The EDII-PW may serve as a non-invasive and relatively low-cost dietary assessment tool that could contribute to maternal risk stratification. However, external validation and calibration assessment are required before clinical application. Future research could explore the relationship between EDII-PW and other health outcomes, such as postpartum depression and recovery, providing further evidence for its application.

Of note, the original EDII-PW consistently outperformed the alternative version that included vitamins C, D, and E. This finding may seem counterintuitive but has several plausible explanations. First, self-reported supplement use is prone to substantial recall bias and measurement error, adding non-differential misclassification that would attenuate true associations towards the null. Second, the protective effects of a diet rich in fruits, vegetables, and whole grains may not be fully explained by these few vitamins alone, as other phytochemicals, fiber, and the synergistic effects of the entire food matrix likely play a crucial role. Third, the nutrient version included more variables, which may have led to overfitting to the development

cohort of MIH-I. Our results suggest that a whole-food approach, rather than a nutrient-focused one, may be more effective for predicting inflammation-related pregnancy outcomes. The three sub-cohorts were recruited over different calendar periods, during which maternal demographic characteristics, socioeconomic conditions, dietary availability, lifestyle factors, and clinical practices may have changed. Although the cohorts were recruited from the same principal clinical centers and used harmonized eligibility criteria and data-collection procedures, the distributions of several baseline characteristics and their trends across EDII-PW quartiles were not identical. Such heterogeneity may influence the baseline risk of adverse outcomes, the strength of diet–biomarker associations, and model calibration. The use of later sub-cohorts for biomarker validation and outcome evaluation provides an assessment of temporal transportability; however, it does not eliminate residual cohort effects.

5. Strengths and limitations

The use of three sub-cohorts, six biomarkers, a previously validated dietary assessment instrument, standardized data collection, and extensive covariate information are important strengths. Several limitations should nevertheless be considered. First, although the culturally adapted FFQ demonstrated acceptable validity against repeated 24-hour dietary recalls and satisfactory reliability among pregnant women, dietary intake remained self-reported and may therefore be subject to recall bias, portion-size estimation error, and residual measurement error. Second, diet was assessed at one time point and may not capture changes across pregnancy or seasons. Third, biomarkers were measured at a single time point and may be affected by transient physiological or clinical conditions. In addition, the EDII-PW was derived using three selected circulating markers of systemic inflammation and did not incorporate oxidative-stress biomarkers, soluble cytokine receptors, anti-inflammatory cytokines, or direct measures of placental inflammation. Therefore, the index may not capture all diet-related inflammatory pathways operating during pregnancy. Fourth, the food-group weights were derived in the MIH population and should not be transported directly to other ethnic or geographic populations without external validation. Recalibration or re-estimation may be required where dietary distributions, food composition, genetic background, environmental exposures, or assay procedures differ. Fifth, the study did not directly compare the predictive performance of EDII-PW with individual or combined circulating biomarkers in the same independent outcome cohort. Finally, residual confounding remains possible because some covariates were self-reported and not all relevant determinants could be measured. In addition, temporal differences among the three recruitment periods may have introduced cohort effects that were not completely controlled by covariate adjustment. Consequently, the temporal stability and calibration of the EDII-PW should be reassessed in future populations. Event counts and EPV ratios are summarized in Supplemental Table 10. For outcomes with relatively few events, the corresponding AUC estimates should be interpreted as exploratory and require confirmation in larger cohorts.

Ridge penalization and bootstrap internal validation can reduce coefficient instability and quantify optimism but cannot compensate fully for the limited number of outcome events. Accordingly, the

low-birth-weight model and the other low-EPV models should remain exploratory even if the sensitivity analyses show similar discrimination.

6. Conclusions

The EDII-PW, a hypothesis-driven dietary inflammation index for pregnant women in the second trimester, has been validated across three sub-cohorts using three inflammatory and three endothelial biomarkers. It may offer valuable insights into predicting maternal and neonatal health outcomes, suggesting its potential utility in assessing dietary inflammation during pregnancy.

Conflict of interest

All the authors declare that they have no competing interests.

The adjusted ROC curves were constructed using participant-specific predicted probabilities obtained from separate multivariable logistic regression models. Each model included one dietary inflammatory index and the same prespecified covariates.

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