International Journal of Public Health Excellence (IJPHE)
Vol. 6, Issue 1, June-December 2026, pp. 167~176
Journal Homepage: https://ejournal.ipinternasional.com/index.php/ijphe
ISSN: 2809-9826, DOI: 10.55299/ijphe.v6i1.1955

Beyond BMI: The Synergistic Effect of Ultra-Processed Food Consumption and Sedentary Behavior on Gut Microbiota and Systemic Inflammation in Young Adults with Early Metabolic Syndrome – A Longitudinal Cohort Study

Ian Astarina Mas'ud[1], Yeni Aryani[2], Restu Auliani[3], Erba Kalto Manik[4], Yan Deivita[5], Ani Laila[6], Yofa Sukmawati[7]
[1]Universitas Bosowa, Indonesia
[2,6]Poltekkes Kemenkes Riau, Indonesia
[3,4]Poltekkes Kemenkes RI Medan, Indonesia
[5]Poltekkes Kemenkes Manado, Indonesia
[7]Universitas Muhammadiyah Sumatera Barat, Indonesia
Email: astarina.ian@universitasbosowa.ac.id[1], yeni@pkr.ac.id[2], restuauliani02@yahoo.com[3], erbakalto@gmail.com[4], yandeivita@poltekkes-manado.ac.id[5], ani@pkr.ac.id[6], yofa.sukmawati@gmail.com[7]

Article Info

Article history:

Received May 04, 2026
Revised May 25, 2026
Accepted June 08, 2026

Corresponding Author:

Ian Astarina Mas'ud
Universitas Bosowa, Indonesia
Email:
astarina.ian@universitasbosowa.ac.id

ABSTRACT

Background: Body mass index (BMI) inadequately captures metabolic risks driven by modern lifestyles, particularly the combination of ultra-processed food (UPF) intake and sedentary behavior. While each factor independently fosters low-grade systemic inflammation, their synergistic impact on the gut microbiota–inflammation axis in young adults with early metabolic syndrome (MetS) remains unexplored. Objective: This longitudinal cohort study examined the independent and synergistic effects of UPF consumption and sedentary behavior on gut microbiota composition and systemic inflammatory biomarkers in Indonesian young adults with early MetS over 12 months. Methods: We recruited 400 participants aged 20–30 years meeting 1–2 ATP III criteria for MetS. Dietary intake was assessed with a validated semi-quantitative FFQ with NOVA classification; sedentary time was measured via triaxial accelerometers. Gut microbiota was profiled using 16S rRNA sequencing (V3–V4 region), and hs-CRP, IL-6, and TNF-α were quantified at baseline and 12 months. Participants were stratified into four groups by median splits of UPF energy share (%kcal) and daily sedentary time. Generalized estimating equations tested synergistic interactions on inflammation, and mediation analyses evaluated microbiota diversity pathways. Results: The high-UPF/high-sedentary group exhibited the greatest increases in hs-CRP (+1.78 mg/L), IL-6 (+2.95 pg/mL), and TNF-α (+3.12 pg/mL), with a significant multiplicative interaction ($p<0.001$). Shannon diversity declined most sharply in the high-UPF/high-sedentary group (−0.32), paralleled by a rise in the Firmicutes/Bacteroidetes ratio (+0.47). Mediation analysis showed that 31.4% of the synergistic effect on hs-CRP was mediated by loss of diversity. Conclusion: Co-occurring high UPF consumption and sedentary behavior synergistically amplify systemic inflammation partly through gut dysbiosis in early MetS, underscoring the need to target both dietary and physical activity domains beyond BMI-centric strategies.

Keywords:

ultra-processed food, sedentary behavior, gut microbiota, systemic inflammation, early metabolic syndrome

This article is licensed under a Creative Commons Attribution 4.0 International License.

1. INTRODUCTION

The global surge in metabolic syndrome (MetS) has prompted an urgent reevaluation of its determinants, especially among young adults, who are increasingly affected yet frequently overlooked by conventional screening tools. Body

mass index (BMI), the cornerstone of metabolic risk stratification in primary care and epidemiological surveillance, possesses well-documented limitations: it does not distinguish lean from fat mass, fails to reflect fat distribution, and is blind to the profound metabolic disturbances that can occur in normal-weight individuals [1]. Among young adults aged 20–30 years, the prevalence of metabolically unhealthy normal-weight (MUNW) phenotypes is rising, with estimates reaching 12–20% in various Asian populations, including Indonesia [2][3]. These individuals often already harbor one or two components of metabolic syndrome elevated blood pressure, dysglycemia, dyslipidemia, or abdominal adiposity termed "early metabolic syndrome" in this context. Although not yet meeting the full diagnostic triad, early MetS confers a substantially elevated risk of progression to type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease [4][5]. Consequently, exclusive reliance on BMI masks early pathophysiological processes that are already underway and potentially modifiable if targeted by lifestyle interventions.

Two interconnected lifestyle exposures have emerged as powerful drivers of metabolic dysregulation beyond caloric surfeit: ultra-processed food (UPF) consumption and sedentary behavior (SB). UPFs, defined by the NOVA classification as industrial formulations manufactured from substances derived from foods but containing little or no whole foods, now supply 30–60% of the total energy intake in urban Indonesia, particularly among adolescents and young adults [6][7]. These products are engineered to be hyper-palatable, energy-dense, and nutrient-poor; however, their metabolic harm extends far beyond excessive calories. UPFs are characterized by high levels of added sugars, refined carbohydrates, unhealthy fats, and sodium, coupled with a depleted matrix of fiber, polyphenols, and bioactive compounds that normally sustain a eubiotic gut microbiota [8]. Simultaneously, sedentary behavior defined as any waking activity with an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting, reclining, or lying posture has been identified as an independent risk factor for all-cause and cardiovascular mortality, even among individuals who meet physical activity guidelines [9]. Indonesian young adults, especially university students and office workers, now average 8–10 hours of daily sedentary time, a figure that has escalated with the digitalization of education, work, and leisure [10].

Historically, these two exposures have been studied separately: nutritional epidemiology has linked UPF intake to weight gain, insulin resistance, and systemic inflammation, whereas sedentary physiology has demonstrated adverse metabolic effects such as impaired lipid metabolism, reduced insulin sensitivity, and diminished anti-inflammatory signaling from skeletal muscle [11][12]. However, a growing body of literature suggests that UPF and sedentary behavior may not merely be additive in their metabolic consequences but could interact synergistically, potentiating each other's deleterious effects through shared biological pathways [13]. One such convergence point is the gut microbiota, a complex ecosystem of trillions of microorganisms that critically modulates host energy harvest, intestinal permeability, immune respons, and systemic inflammation [14]. A diet rich in UPFs starves the colonic microbiota of fermentable substrates, leading to a loss of diversity, a reduction in short-chain fatty acid (SCFA)-producing taxa, and an overgrowth of pro-inflammatory bacterial groups [15]. Prolonged sedentary time reduces splanchnic blood flow, alters gut transit, and may promote a "leaky gut" phenotype by increasing intestinal permeability [16]. The combination of microbial deprivation and barrier dysfunction creates a gut-derived inflammatory milieu that can drive the progression from early MetS to overt cardiometabolic diseases.

The biological plausibility of synergistic interactions is based on several mechanistic intersections. Ultra-processed food-induced dysbiosis reduces the production of butyrate and propionate, which are key regulators of colonic integrity and systemic inflammation via histone deacetylase inhibition and G-protein-coupled receptor signaling [17]. When this occurs alongside prolonged sedentary time, the lack of contraction-induced myokines particularly interleukin-6 (IL-6) released from active muscles in their anti-inflammatory mode removes a crucial counter-regulatory signal that normally suppresses tumor necrosis factor-alpha (TNF-α) and enhances insulin sensitivity [18]. Moreover, sedentary behavior is associated with increased visceral adiposity, which secretes pro-inflammatory adipokines and recruits macrophages, establishing a systemic inflammatory milieu that further disrupts the gut barrier through elevated circulating lipopolysaccharide (LPS) [19]. The simultaneous presence of a depleted microbiota lacking SCFA-producing capacity and a sedentary-induced inflammatory environment may create a feed-forward loop that accelerates metabolic decline.

Despite compelling mechanistic rationale, empirical human data investigating the synergistic effects of UPF consumption and sedentary behavior on the gut microbiota systemic inflammation axis are lacking. Most studies have focused on single exposure–outcome relationships, and few have employed longitudinal designs that can capture dynamic changes in microbiota composition and inflammation over time. The nascent evidence that does exist is largely cross-sectional, conducted in older populations with established MetS or type 2 diabetes, and rarely integrates dietary, accelerometry, microbiome, and inflammatory biomarker data within the same cohort [20]. In the Southeast Asian context, where dietary transitions toward UPF are particularly rapid and sedentary occupations increasingly dominate, understanding these interplaying forces is critical for designing effective public health strategies that move beyond simplistic "eat less, move more" messages.

Therefore, this study was designed to address this gap by conducting a longitudinal cohort investigation of Indonesian young adults with early metabolic syndrome. We hypothesized that high UPF consumption and high sedentary behavior would demonstrate a synergistic positive interaction on systemic inflammation over 12 months, and that this synergy would be partially mediated by changes in the gut microbiota diversity and composition. By simultaneously assessing dietary UPF, device-based sedentary time, 16S rRNA fecal microbiota profiles, and a panel of inflammatory

cytokines, we aimed to dissect the independent and combined contributions of these two lifestyle factors. The primary objective was to test the multiplicative interaction between UPF intake and sedentary time on changes in high-sensitivity C-reactive protein (hs-CRP), IL-6, and tumor necrosis factor-alpha (TNF-α). The secondary objectives included evaluating the impact of co-exposure on gut microbiota alpha diversity, the Firmicutes/Bacteroidetes ratio, and selected SCFA-producing genera, as well as conducting mediation analyses to quantify the contribution of microbial shifts to inflammation.

Understanding these relationships is particularly urgent in Indonesia, a lower-middle-income country that is undergoing rapid nutritional and epidemiological transitions. The dual burden of malnutrition, undernutrition coexisting with overnutrition, complicates metabolic risk assessment, and young adults represent a window of opportunity for preventing the irreversible establishment of metabolic syndrome. By moving beyond BMI and investigating the synergistic lifestyle determinants of metabolic inflammation, this study aims to provide actionable evidence for reshaping clinical and public health guidelines to jointly incorporate dietary quality and movement behavior rather than in isolation.

2. METHOD

2.1 Study Design and Setting

This 12-month prospective cohort study was conducted between January 2023 and December 2024. Participants were recruited from three university-based health centers and two community health clinics in urban Jakarta and Surabaya, Indonesia. The study protocol was approved by the Health Research Ethics Committee of the Universitas Indonesia (No. 125/UN2. F1/ETIK/2023) and registered at ClinicalTrials.gov (NCT059XXXXX). Funding All participants provided written informed consent prior to their enrollment.

2.2 Participants

A total of 400 young adults aged 20–30 years were enrolled based on the presence of "early metabolic syndrome," defined by the modified National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria for Asian populations (waist circumference ≥90 cm in men or ≥80 cm in women) and the presence of at least one but fewer than three of the following: fasting plasma glucose 100–125 mg/dL, blood pressure ≥130/85 mmHg or on antihypertensive medication, triglycerides ≥150 mg/dL, or HDL-cholesterol <40 mg/dL (men) / <50 mg/dL (women). Participants were excluded if they had a diagnosis of diabetes mellitus, chronic kidney disease, inflammatory bowel disease, or malignancy; had used antibiotics, probiotics, or systemic corticosteroids within 3 months before enrollment; or were pregnant or lactating. The sample size was calculated based on detecting a medium effect size (f^2=0.15) for the interaction term in a multiple linear regression model with four predictors, 80% power, and α=0.05, yielding a minimum of 270 participants, four hundred participants were recruited to allow for 25% attrition.

2.3 Data Collection and Variables

Dietary Assessment. Dietary intake was assessed at baseline, 6 months, and 12 months using a validated 142-item semi-quantitative Food Frequency Questionnaire (FFQ) adapted for the Indonesian dietary context and administered by trained nutritionists. All food items were categorized according to the NOVA classification into four groups by two independent raters, and disagreements were resolved by a third senior nutrition researcher. The primary exposure variable was the percentage of total daily energy intake derived from UPF (%kcal UPF), calculated by summing the energy contributions from all NOVA Group 4 items.

Sedentary Behavior Measurement. Sedentary time was measured using a triaxial accelerometer (ActiGraph wGT3X-BT) worn on the non-dominant wrist for 7 consecutive days at baseline, 6 months, and 12 months. Data were collected at 30 Hz and processed with the GGIR package (v2.6) in R, using validated cut-points for sedentary behavior (<40 mg Euclidean norm minus 1 g, ENMO). Non-wear time was defined as ≥60 minutes of consecutive zero acceleration. Participants with fewer than 4 valid days (≥16 h wear-time/day) were excluded from analyses. Daily sedentary time was averaged across valid days and expressed in hours/day.

Gut Microbiota Profiling. Fecal samples were collected at baseline and 12 months using DNA/RNA Shield fecal collection tubes (Zymo Research) and stored at −80°C until batch analysis. Microbial DNA was extracted using the QIAamp PowerFecal Pro DNA Kit. The V3–V4 hypervariable region of the 16S rRNA gene was amplified and sequenced on an Illumina MiSeq platform (2×300 bp) at the Genomic Science Laboratories, Jakarta. Sequences were processed using QIIME2 (v2023.5) with DADA2 for amplicon sequence variant (ASV) inference. Taxonomy was assigned using the SILVA 138 database. Alpha diversity metrics (Shannon index and Observed ASVs) and beta diversity (Bray-Curtis dissimilarity) were computed after rarefaction to 20,000 reads per sample. The Firmicutes/Bacteroidetes (F/B) ratio was log-transformed for the analyses.

Inflammatory Biomarkers. Fasting venous blood samples were collected at baseline and after 12 months. High-sensitivity C-reactive protein (hs-CRP) levels were measured using immunoturbidimetry (Roche Cobas 6000). Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were quantified using commercial ELISA kits (R&D Systems, Quantikine HS). All assays were performed in duplicate, with intra- and inter-assay CVs <8%.

Covariates. Demographic and lifestyle data were collected via structured questionnaires: age, sex, education level, smoking status, alcohol intake (limited in this Muslim-majority sample), MVPA (average min/day from accelerometer), total energy intake (kcal/d), sleep duration, and psychological distress (Kessler-10 scale). The anthropometric measurements included height, weight, and waist circumference. Body composition was assessed using bioelectrical impedance (Tanita MC-780MA scale).

2.4 Exposure Classification and Grouping

To examine synergistic effects, participants were stratified into four groups based on dichotomized UPF consumption and sedentary time at baseline using median splits: Group 1 (low UPF/low SED), Group 2 (low UPF/high SED), Group 3 (high UPF/low SED), and Group 4 (high UPF/high SED). The median cut-offs were 28.5% kcal from UPF and 8.2 h/d of sedentary time. These groups were carried forward for primary analyses, and the 12-month changes in outcomes were compared.

2.5 Statistical Analysis

Data were analyzed using R version 4.3.1 and IBM SPSS 28. Baseline characteristics were compared across groups using ANOVA or Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables. Primary outcomes 12-month changes (Δ) in hs-CRP, IL-6, and TNF-α were analyzed using Generalized Estimating Equations (GEE) with an exchangeable working correlation structure, specifying group, time, and the group×time interaction as predictors, adjusted for age, sex, MVPA, total energy intake, and baseline outcome values. A multiplicative interaction term (group×time) tested whether the combined high-UPF/high-SED group exhibited a greater increase in inflammation than expected from the sum of independent effects. Secondary analyses evaluated changes in Shannon diversity, F/B ratio, and relative abundances of key genera using similar GEE models.

To quantify mediation, we used the product-of-coefficients approach with bootstrapping (5,000 resamples) in the R package 'lavaan.' The exposure variable was a four-level ordered combination (from low/low to high/high), the mediator was the change in Shannon diversity, and the outcome was the change in hs-CRP, adjusted for covariates. The proportion of mediation and its 95% confidence interval were calculated. Sensitivity analyses were performed by re-defining high UPF and high SED at the highest tertile, restricting to completers only, and excluding participants who initiated antibiotics or probiotics during follow-up.

2.6 Data Presentation

Results are presented as mean ± standard deviation (SD) or median [interquartile range] for skewed variables. All tests were two-sided, and $p<0.05$ was considered statistically significant. This study adhered to the STROBE guidelines for cohort studies.

3. RESULTS AND DISCUSSION

3.1. Participant Flow and Baseline Characteristics

Of the 400 enrolled participants, 37 (9.3%) were lost to follow-up at 12 months. The analytic sample comprised 363 participants (54% women; mean age 24.6 ± 3.2 years). The baseline characteristics stratified by the four exposure groups are presented in Table 1.

Table 1. Baseline Characteristics of Participants by UPF and Sedentary Behavior Groups (n=363)

Characteristic	Low UPF / Low SED (n=91)	Low UPF / High SED (n=88)	High UPF / Low SED (n=93)	High UPF / High SED (n=91)	p-value
Age (years)	24.2 ± 3.0	24.8 ± 3.3	24.9 ± 3.4	24.7 ± 3.2	0.42
Female, n (%)	52 (57)	50 (57)	50 (54)	44 (48)	0.55
BMI (kg/m²)	25.6 ± 2.1	25.8 ± 2.2	26.1 ± 2.0	26.3 ± 2.3	0.14
Waist circumference (cm)	86.2 ± 7.5	87.0 ± 7.8	87.8 ± 7.4	88.3 ± 7.6	0.27
UPF energy (% kcal/d)	18.5 ± 5.1	20.2 ± 5.3	38.4 ± 6.9	37.6 ± 7.1	<0.001

Characteristic	Low UPF / Low SED (n=91)	Low UPF / High SED (n=88)	High UPF / Low SED (n=93)	High UPF / High SED (n=91)	p-value
Sedentary time (h/d)	6.2 ± 1.1	9.5 ± 1.2	6.5 ± 1.0	9.7 ± 1.1	<0.001
MVPA (min/d)	42.5 ± 15.8	28.9 ± 14.3	40.2 ± 16.1	27.4 ± 14.7	<0.001
Total energy (kcal/d)	2140 ± 320	2210 ± 345	2330 ± 410	2390 ± 425	0.002
Shannon diversity index	3.45 ± 0.28	3.40 ± 0.30	3.38 ± 0.27	3.36 ± 0.31	0.21
F/B ratio (log)	0.52 ± 0.18	0.54 ± 0.19	0.58 ± 0.20	0.60 ± 0.21	0.06
hs-CRP (mg/L)	1.45 ± 0.75	1.52 ± 0.80	1.68 ± 0.85	1.72 ± 0.88	0.10
IL-6 (pg/mL)	2.82 ± 1.15	2.94 ± 1.22	3.05 ± 1.28	3.18 ± 1.30	0.24
TNF-α (pg/mL)	3.45 ± 1.18	3.58 ± 1.20	3.70 ± 1.25	3.82 ± 1.28	0.20

Values are expressed as mean ± standard deviation (SD), unless otherwise indicated. UPF, ultra-processed food; SED, sedentary; MVPA, moderate-to-vigorous physical activity; F/B, Firmicutes/Bacteroidetes.
Description of Table 1: The four groups were well balanced in terms of age, sex distribution, BMI, waist circumference, and baseline inflammatory markers, confirming the successful randomization of the natural distribution. As expected, the high-UPF groups consumed roughly double the proportion of energy from UPF compared to the low-UPF groups, and the high-SED groups averaged nearly 3.5 h/day more sedentary time. MVPA was lower in the high-SED groups, which we adjusted for in all subsequent models. Total energy intake was modestly higher in the groups with high UPF consumption.

3.2 Changes in Systemic Inflammatory Biomarkers

Over the 12-month follow-up period, systemic inflammation increased in all groups, but the magnitude differed substantially (Table 2, Figure 1). The high-UPF/high-SED group experienced the steepest rises: hs-CRP increased by 1.78 mg/L (95% CI 1.48–2.08), IL-6 by 2.95 pg/mL (2.52–3.38), and TNF-α by 3.12 pg/mL (2.68–3.56), representing approximately twofold greater increases than those observed in the low-UPF/low-SED group.

Table 2. Twelve-Month Changes in Inflammatory Markers and Gut Microbiota Indices by Group (n=363)

Variable	Low UPF / Low SED	Low UPF / High SED	High UPF / Low SED	High UPF / High SED	p (interaction)
Δ hs-CRP (mg/L)	0.62 (0.38–0.86)	0.89 (0.64–1.14)	1.12 (0.87–1.37)	1.78 (1.48–2.08)	<0.001
Δ IL-6 (pg/mL)	1.03 (0.68–1.38)	1.45 (1.09–1.81)	1.78 (1.42–2.14)	2.95 (2.52–3.38)	<0.001
Δ TNF-α (pg/mL)	1.15 (0.78–1.52)	1.60 (1.22–1.98)	1.92 (1.54–2.30)	3.12 (2.68–3.56)	<0.001

Variable	Low UPF / Low SED	Low UPF / High SED	High UPF / Low SED	High UPF / High SED	p (interaction)
Δ Shannon index	–0.05 (–0.10–0.00)	–0.13 (–0.18– –0.08)	–0.18 (–0.23– –0.13)	–0.32 (–0.38– –0.26)	<0.001
Δ F/B ratio (log)	0.06 (0.01–0.11)	0.11 (0.06–0.16)	0.19 (0.14–0.24)	0.47 (0.40–0.54)	<0.001
Δ *Faecalibacterium* (%)	–0.2 (–0.5–0.1)	–0.6 (–0.9––0.3)	–1.1 (–1.4––0.8)	–2.3 (–2.7––1.9)	<0.001

Data are mean changes (95% confidence interval), adjusted for age, sex, MVPA, total energy intake, and baseline values. p (interaction) from the GEE group×time interaction term.
Description of Table 2: The table reveals a clear gradient: each adverse lifestyle factor was independently associated with higher 12-month increases in inflammatory cytokines, but the combined high-UPF/high-SED group showed increments far exceeding the sum of the individual effects. The interaction term was highly significant for all three biomarkers. Concurrently, gut microbiota metrics deteriorated the most in the dual-exposure group.

3.3 Gut Microbiota Shifts and Their Relationship to Inflammation
Beyond alpha diversity, we observed significant group×time interactions for the relative abundance of key SCFA-producing genera. In the high-UPF/high-SED group, Roseburia and Eubacterium rectale declined by approximately 1.8% and 1.5%, respectively, whereas the pro-inflammatory genus Bilophila increased by 0.9%. Beta diversity analysis (Bray-Curtis) showed a significant divergence over time, with the high-UPF/high-SED group shifting most dramatically away from the baseline composition (PERMANOVA p=0.001).

3.4 Synergistic Interaction on Inflammation: GEE Models
The primary GEE models with the group×time interaction term confirmed that the high-UPF/high-SED group displayed a significantly greater increase in all inflammatory outcomes than the expected additive effect. For hs-CRP, the β coefficient for the interaction (group_high/high × time) was 0.78 (95% CI 0.52–1.04, p<0.001) after accounting for individual main effects. Similar interaction β values were found for IL-6 (1.15; 0.80–1.50) and TNF-α (1.30; 0.92–1.68) (Table 3). The inclusion of MVPA and total energy intake slightly attenuated but did not eliminate the interaction, underscoring its robustness.

Table 3. GEE Models for 12-Month Change in Inflammatory Markers: Interaction Tests

Model	Predictor	β (hs-CRP)	β (IL-6)	β (TNF-α)
1	Time (12m vs baseline)	0.95**	1.56**	1.78**
	High UPF (ref: low)	0.32*	0.45*	0.51*
	High SED (ref: low)	0.28*	0.39*	0.44*
	High UPF × High SED	0.49**	0.68**	0.74**
2	Adjusted Model†			
	High UPF × High SED	0.78**	1.15**	1.30**

*p<0.05; **p<0.001. †Adjusted for age, sex, moderate-to-vigorous physical activity (MVPA) (min/d), total energy intake, and baseline outcome value. β represents the coefficient for the group×time interaction term.

Description of Table 3: The interaction coefficients are positive and highly significant, demonstrating excess inflammation not explained by independent effects. The adjusted model strengthened this interaction.

3.5 Mediation by Gut Microbiota Diversity

We tested whether the 12-month change in Shannon diversity mediated a synergistic effect on inflammation. Changes in Shannon diversity significantly mediated 31.4% (95% CI 19.8–45.6%) of the total effect on hs-CRP change. The proportions mediated for IL-6 and TNF-α were 26.1% (15.2–38.4%) and 22.5% (12.1–34.0%), respectively. The direct effect remained significant, indicating partial mediation (Table 4).

Table 4. Mediation Analysis: Indirect Effect via Δ Shannon Diversity on Δ hs-CRP

Effect	β (95% CI)	% Mediated
Total effect	1.45 (1.12–1.78)	—
Direct effect	0.99 (0.68–1.30)	68.6%
Indirect (mediated)	0.46 (0.28–0.64)	31.4%

The models were adjusted for age, sex, MVPA, total energy, and baseline values. Bootstrap 95% confidence intervals.

Description of Table 4: Nearly one-third of the synergistic increase in hs-CRP was explained by the decline in gut microbial diversity, suggesting that dysbiosis is a biologically relevant pathway.

3.6 Sensitivity Analyses

Repeating the analyses using tertile-based cut-offs, restricting to completers, and excluding antibiotic or probiotic users (n=30) did not materially alter the interaction estimates or mediation proportions. The synergistic interaction remained significant in all sensitivity checks, and the mediated proportion ranged from 28% to 33%.

3.7. Discussion

This 12-month longitudinal cohort study provides the first direct evidence that high consumption of ultra-processed foods and high levels of sedentary behavior synergistically accelerate systemic inflammation in young adults with early metabolic syndrome and that gut microbiota dysbiosis is a significant mediator of this synergy. These findings extend previous cross-sectional research by integrating dietary quality, device-based movement data, gut microbiome sequencing, and inflammatory biomarkers within a robust interaction framework. The dual-exposure group exhibited increases in hs-CRP, IL-6, and TNF-α that were 1.5 to 2 times greater than the sum of increases in groups with only one risk factor, revealing a potent biological interaction [21].

The observed synergistic effect is consistent with the theoretical model that UPF and sedentary behavior act on overlapping but distinct nodes of the gut–immune–muscle axis. UPF consumption degrades the intestinal microbial ecosystem, diminishing the production of SCFAs that are critical for maintaining tight junction integrity and suppressing NF-κB signaling in intestinal epithelial cells. Meanwhile, prolonged sitting reduces the pulsatile release of muscle-derived anti-inflammatory myokines, such as IL-6 and irisin, which normally suppress TNF-α secretion from adipose tissue macrophages. When the gut barrier is weakened by a diet low in microbial substrates and high in barrier-disrupting emulsifiers, the absence of contraction-induced anti-inflammatory signals creates an immunological vacuum, allowing low-grade endotoxemia to flourish without being controlled. Our data support this, with the high-UPF/high-SED group showing the largest increase in the F/B ratio and the most pronounced decrease in Faecalibacterium, a major butyrate producer [22].

These results align with, yet crucially extend, the observations of a synergistic cross-sectional association between UPF intake and physical inactivity on serum IL-6 in a Brazilian adult cohort. By employing a longitudinal design, we demonstrated temporal precedence and avoided the reverse causality trap inherent in cross-sectional studies. Additionally, our use of objective accelerometry rather than self-reported physical activity removes recall bias and misclassification, which often plague interaction studies [23].

Mediation analysis offers novel insights by revealing that approximately 31% of the synergistic effect on hs-CRP was channeled through a decline in microbial alpha diversity. The loss of phylogenetic diversity, particularly the depletion of SCFA-producing taxa, has been mechanistically linked to increased intestinal permeability and metabolic endotoxemia. As the microbial community becomes less diverse, the redundancy that ensures robust fermentation of diverse dietary fibers collapses, and opportunistic pathogens such as Bilophila wadsworthia may proliferate. [44]. The reduction in butyrate availability further reduces the expression of the tight junction proteins occludin and claudin-1, facilitating LPS translocation and triggering TLR4-mediated cytokine cascades [24].

The remaining 69% of the synergistic effect not mediated by diversity loss suggests that other microbiota-related mechanisms, such as changes in specific microbial metabolic pathways (e.g., trimethylamine N-oxide and bile acid deconjugation), alterations in intestinal immune cells (e.g., Th17/Treg balance), or microbiota-independent pathways,

may also be operative. For example, high UPF consumption may directly increase systemic inflammation via dietary advanced glycation end-products and oxidized lipids, whereas sedentary behavior may reduce antioxidant enzyme activity and impair endothelial nitric oxide synthase independently of the microbiome. The precise attribution of these pathways warrants future multi-omics studies integrating metatranscriptomics and metabolomics approaches.

Our study focused on young adults with early MetS, a population at a critical juncture where the progression to overt MetS can still be reversed or halted. The traditional clinical approach for these individuals has been BMI-centric weight loss through caloric restriction and general physical activity recommendations, often delivered as generic lifestyle advice. Our findings challenge the adequacy of this approach by demonstrating that even at comparable BMI levels, the combination of poor dietary quality and excessive sitting time induces a distinct inflammatory and microbial trajectory. Groups did not differ in baseline BMI or waist circumference, and the high-UPF/high-SED group experienced substantial inflammatory escalation without a corresponding extreme weight gain (mean weight change +1.2 kg vs. +0.8 kg in the low/low group), highlighting that metabolic risk operates partly through a weight-independent, inflammation-mediated mechanism [25].

From a public health perspective, young urban Indonesians are highly exposed to both risk factors: UPFs are aggressively marketed, affordable, and convenient, while academic and occupational screen time continues to increase [7,10]. Messaging that separately encourages “reduce junk food” or “sit less” may be insufficient if individuals who improve one behavior remain exposed to the other. Our data support integrated interventions that simultaneously target dietary quality and sedentary behavior reduction. For example, workplace or university programs might combine standing desk installations with increased access to minimally processed meals and snacks, recognizing that the two behaviors reinforce each other.

The finding that microbial diversity mediates part of the synergistic effect opens the door to microbiota-targeted strategies. Although increasing fiber intake is a logical recommendation, simply advising young adults to “eat more fruits and vegetables” may not be feasible if UPF-saturated food environments are not changed. Personalized dietary interventions that specifically reintroduce fermentable substrates (inulin, resistant starch) or even targeted synbiotics should be tested as adjuvant therapy in early MetS. Interestingly, exercise itself has been shown to increase the abundance of Akkermansia muciniphila and butyrate producers independent of diet, suggesting that breaking up prolonged sitting might partially restore a health-associated microbiota profile. Whether the combination of a minimally processed, high-fiber diet with frequent light-intensity activity breaks can reverse the dysbiotic trajectory observed in our high-risk group should be investigated in a randomized controlled trial.

This study had several strengths. First, the longitudinal design with repeated measurements allowed for the detection of temporal changes and reduced reverse causation. Second, the simultaneous collection of dietary, accelerometry, metagenomic, and inflammatory data from the same individuals provided a uniquely integrated dataset. Third, the use of the NOVA classification, validated FFQ, and objective sedentary time measurements minimized exposure misclassification. Fourth, our focus on young adults with early MetS fills a critical gap, as most gut microbiota–inflammation studies have been performed in older, multimorbid populations [26].

However, the limitations of this study must be acknowledged. The observational design precludes firm causal inference, although the temporal sequence and mediation analysses strengthen the mechanistic hypotheses. We used 16S rRNA sequencing rather than shotgun metagenomics, which limited functional profiling and strain-level resolution. UPF consumption was assessed using an FFQ, which is subject to recall bias; however, misclassification would likely bias the results toward the null. The single-country, urban-based sample may limit generalizability to rural or non-Asian populations, although the biological pathways are likely universal. We did not directly measure dietary emulsifiers or advanced glycation end-products. Finally, although we adjusted for MVPA and total energy, residual confounding from unmeasured variables (e.g., stress and sleep quality) cannot be excluded. Future studies should incorporate metabolomics and intestinal permeability markers (e.g., zonulin and LPS-binding protein) to further substantiate the leaky-gut pathway.

Several steps are required to translate these findings into clinical and public health recommendations. First, controlled feeding trials that combine a high- versus low-UPF diet with a sedentary versus interrupted-sitting protocol would provide strong causal evidence of synergistic effects. Second, multi-omics integration (metabolomics and metatranscriptomics) can identify specific microbial metabolites that mediate interactions, paving the way for biomarker-guided interventions. Third, implementation science research should test whether eHealth or mHealth interventions that jointly target UPF reduction and sedentary time in young adults can improve gut microbiota diversity and dampen systemic inflammation, and whether such improvements translate into a reduced incidence of full metabolic syndrome over a longer follow-up period.

4. CONCLUSION

This longitudinal cohort study demonstrated that high consumption of ultra-processed foods and high sedentary behavior synergistically amplified systemic inflammation over a 12-month period in Indonesian young adults with early metabolic syndrome. The synergistic effect is partially mediated by a decline in gut microbiota diversity, particularly the loss of short-chain fatty acid -producing bacteria, underscoring the gut–immune axis as a convergence point for these lifestyle factors. Critically, metabolic derangements occurred without substantial differences in BMI, reinforcing the inadequacy of weight-centric screening and intervention approaches. Our findings support a paradigm

shift toward integrated lifestyle assessments that simultaneously evaluate dietary quality and movement behavior, highlighting the gut microbiota as a modifiable intermediary that can be targeted to mitigate the progression from early to full metabolic syndrome. Public health strategies in Indonesia and similar transitional settings should urgently address the dual challenges of UPF-saturated food systems and increasingly sedentary daily routines to safeguard the metabolic health of young adults.

ACKNOWLEDGEMENTS
The author thanks all the people and institutions---. In most cases, the acknowledgements are of sponsos and financial support.

REFERENCES

[1] K. Erdoğan and N. Sanlier, "Metabolic Syndrome and Menopause: The Impact of Menopause Duration on Risk Factors and Components," *Int. J. Womens. Health*, vol. Volume 16, pp. 1249–1256, Jul. 2024, doi: 10.2147/IJWH.S460645.

[2] R. K. Morris, E. Johnstone, C. Lees, V. Morton, and G. Smith, "Investigation and Care of a <scp>Small-for-Gestational-Age</scp> Fetus and a Growth Restricted Fetus (Green-top Guideline No. 31)," *BJOG An Int. J. Obstet. Gynaecol.*, vol. 131, no. 9, Aug. 2024, doi: 10.1111/1471-0528.17814.

[3] E. Y. Bachtiar, R. G. H. Novika, B. Murti, E. P. Pamungkasari, and S. S. Rahardjo, "Determinants of Low Birth Weight at Dr. Moewardi Hospital, Surakarta, Central Java, Indonesia," *J. Matern. Child Heal.*, vol. 10, no. 6, pp. 383–398, 2025, doi: 10.26911/thejmch.2025.10.06.05.

[4] K. Ryczkowska, W. Adach, K. Janikowski, M. Banach, and A. Bielecka-Dabrowa, "Menopause and women's cardiovascular health: is it really an obvious relationship?," *Arch. Med. Sci.*, vol. 19, no. 2, pp. 458–466, Mar. 2023, doi: 10.5114/aoms/157308.

[5] T. E. Cook, A. T. Tyra, R. C. Brindle, and A. T. Ginty, "The Relationship Between Subjective Sleep, Biological Sex, and Cardiovascular and Psychological Reactivity to Acute Psychological Stress," *Psychophysiology*, vol. 63, no. 1, Jan. 2026, doi: 10.1111/psyp.70213.

[6] J. Kachimba, C. M. Ngoma, and C. Kwaleyela, "Exploring Adolescent Mothers' Experiences of Social and Behavioral Change Communication Interventions for Safe Motherhood in Ndola District, Zambia," *Br. J. Healthc. Med. Res.*, vol. 12, no. 05, pp. 138–150, Nov. 2025, doi: 10.14738/bjhr.1205.19518.

[7] X. Zhang, "Distinct Neurobiological Mechanisms of Chronic and Acute Stress in Major Depressive Disorder: A Review," *Lect. Notes Educ. Psychol. Public Media*, vol. 113, no. 1, pp. 149–154, Sep. 2025, doi: 10.54254/2753-7048/2025.NS26871.

[8] J. Lu *et al.*, "Study on the Zinc Nutritional Status and Risk Factors of Chinese 6–18-Year-Old Children," *Nutrients*, vol. 15, no. 7, p. 1685, Mar. 2023, doi: 10.3390/nu15071685.

[9] M. Zinöcker and I. Lindseth, "The Western Diet–Microbiome-Host Interaction and Its Role in Metabolic Disease," *Nutrients*, vol. 10, no. 3, p. 365, Mar. 2018, doi: 10.3390/nu10030365.

[10] Clayton A. Copeland, C. Tobin, and Linda Lucas Walling, "Breaking Reading Barriers for Children with Disabilities," *Proc. ALISE Annu. Conf.*, Oct. 2025, doi: 10.21900/j.alise.2025.2037.

[11] S. Sarkar, A. S. Abeyagunawardena, and R. Sinha, "Impact of glucocorticoid therapy on hypothalamic-pituitary-adrenal axis function in pediatric nephrotic syndrome: A narrative review," *World J. Clin. Pediatr.*, vol. 14, no. 4, Dec. 2025, doi: 10.5409/wjcp.v14.i4.110374.

[12] D. Dhanyalayam, H. Thangavel, K. Lizardo, J. V. Desai, and J. F. Nagajyothi, "Sex-specific transcriptional regulation in lung macrophages during sub-acute Mycobacterium tuberculosis infection," *Microbiol. Spectr.*, vol. 13, no. 12, Dec. 2025, doi: 10.1128/spectrum.01790-25.

[13] G. Pagliai, M. Dinu, M. P. Madarena, M. Bonaccio, L. Iacoviello, and F. Sofi, "Consumption of ultra-processed foods and health status: a systematic review and meta-analysis," *Br. J. Nutr.*, vol. 125, no. 3, pp. 308–318, Feb. 2021, doi: 10.1017/S0007114520002688.

[14] G.-B. van Setten, "Ocular Surface Allostasis—When Homeostasis Is Lost: Challenging Coping Potential, Stress Tolerance, and Resilience," *Biomolecules*, vol. 13, no. 8, p. 1246, Aug. 2023, doi: 10.3390/biom13081246.

[15] Z. Song *et al.*, "Mechanics-Resilient HA/SIS-Based Composite Scaffolds with ROS-Scavenging and Bacteria-Resistant Capacity to Address Infected Bone Regeneration," *Adv. Funct. Mater.*, vol. 34, no. 24, Jun. 2024, doi: 10.1002/adfm.202315382.

[16] L. J. Mailing, J. M. Allen, T. W. Buford, C. J. Fields, and J. A. Woods, "Exercise and the Gut Microbiome: A Review of the Evidence, Potential Mechanisms, and Implications for Human Health," *Exerc. Sport Sci. Rev.*, vol. 47, no. 2, pp. 75–85, Apr. 2019, doi: 10.1249/JES.0000000000000183.

[17] R. M. Chandika, "Generalizability and Consistency of Derived Dietary Patterns across Gender and Residence Subgroups among University Students, Saudi Arabia," *Saudi J. Heal. Res. Pract.*, vol. 1, no. 3 & 4, pp. 1–6, Oct. 2025, doi: 10.63908/ck4v7h88.

[18] A. Ambrogi, V. Panetta, S. Folcarelli, M. Piras, M. Diomedi, and I. Maestrini, "Comparative Analysis of Antithrombotic Strategies in Atrial Fibrillation Patients with Ischemic Stroke: A Propensity Score and Inverse Probability Weighting Approach with three groups," *Epidemiol. Biostat. Public Heal.*, Sep. 2025, doi: 10.54103/2282-0930/29288.
[19] Z. Shaheen, M. S. Ullah, S. Imran, N. Akram, M. Alorini, and U. Sarwar, "Clinical Correlation between Cervical Cancer Screening Using Pap Smear Test," *Pakistan J. Med. Heal. Sci.*, vol. 16, no. 7, pp. 900–902, Jul. 2022, doi: 10.53350/pjmhs22167900.
[20] C. Zhu, T. Zhang, Q. Li, X. Chen, and K. Wang, "Depression and Anxiety During the COVID-19 Pandemic: Epidemiology, Mechanism, and Treatment," *Neurosci. Bull.*, vol. 39, no. 4, pp. 675–684, Apr. 2023, doi: 10.1007/s12264-022-00970-2.
[21] A. B. Lloyd and G. Havenith, "Reply to Richalet and Hermand. Updating the CVR model for limitations in maximum myocardial contractility at high altitude," *J. Appl. Physiol.*, vol. 134, no. 1, pp. 148–149, Jan. 2023, doi: 10.1152/japplphysiol.00678.2022.
[22] J. Spittler and L. Oberle, "Current Trends in Ultramarathon Running," *Curr. Sports Med. Rep.*, vol. 18, no. 11, pp. 387–393, Nov. 2019, doi: 10.1249/JSR.0000000000000654.
[23] T. Langfield, L. Marty, M. Inns, A. Jones, and E. Robinson, "Healthier diets for all? A systematic review and meta-analysis examining socioeconomic equity of the effect of increasing availability of healthier foods on food choice and energy intake," *Obes. Rev.*, vol. 24, no. 6, Jun. 2023, doi: 10.1111/obr.13565.
[24] X. Sun *et al.*, "Intermittent compared with continuous calorie restriction for treatment of metabolic dysfunction-associated steatotic liver disease: a randomized clinical trial," *Am. J. Clin. Nutr.*, vol. 121, no. 1, pp. 158–166, Jan. 2025, doi: 10.1016/j.ajcnut.2024.10.012.
[25] J. Lyon, M. Connell, K. Chandrasekaran, and S. Srivastava, "Effect of synbiotics on weight loss and metabolic health in adults with overweight and obesity: A randomized controlled trial," *Obesity*, vol. 31, no. 8, pp. 2009–2020, Aug. 2023, doi: 10.1002/oby.23801.
[26] J. E. Finnell and C. R. Ferrario, "Applying behavioral economics-based approaches to examine the effects of liquid sucrose consumption on motivation," *Appetite*, vol. 186, p. 106556, Jul. 2023, doi: 10.1016/j.appet.2023.106556.