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RESEARCH ARTICLE

# Fetuin A-Centric Inflammatory Signature Differentiates Latent Metabolic Syndrome Phenotypes in Western Indian Adults: A Community Based Latent Class Analysis

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Abstract: ***Background & objective***: This study aimed to identify latent metabolic phenotypes among Western Indian adults using latent class analysis and to assess the role of inflammatory biomarkers fetuin A, leptin, adiponectin, and interleukin-10 in distinguishing cardiometabolic risk profiles. A secondary aim was to develop a composite index for risk stratification in metabolic syndrome (MetS). ***Methods***: We analysed 400 adults (25–55 years) from Western India. Latent class analysis based on five ATP III indicators identified metabolic phenotypes, with BCH weighting accounting for classification uncertainty. Serum biomarkers were measured by duplicate ELISA. Group differences were assessed via Wald $\chi^2$ tests, biomarker correlations with a 0–5 MetS severity score using Spearman's $\rho$, and independent predictors using multinomial logistic regression. An inflammatory ratio = (leptin + fetuin A)/(adiponectin + IL-10) was computed. ***Results***: A three-class model best fit the data (entropy = 0.90): Central Obesity (40.7 %), Metabolically Healthy (23.0 %), and Full MetS/High Risk (36.3 %). All biomarkers differed significantly across classes ($p < 0.001$). Compared to the healthy phenotype, the high-risk class showed markedly elevated fetuin A (+436 %) and leptin (+170 %), and reduced adiponectin (−47 %) and IL-10 (−41 %). Fetuin A showed the strongest correlation with MetS severity ($\rho = +0.52$). In multivariable models, only fetuin A independently predicted class membership. The composite ratio increased progressively from 0.85 (healthy) to 4.62 (high risk) ($p < 0.001$). ***Conclusions***: Latent class modelling revealed three distinct inflammatory phenotypes. Fetuin A emerged as a dominant marker of cardiometabolic risk, and the composite ratio outperformed individual biomarkers, supporting their use in early MetS risk stratification.

Keywords: Metabolic Syndrome; Latent Class Analysis; Inflammatory Biomarkers; Fetuin A; Leptin; Adiponectin; Interleukin-10 (IL-10); Insulin Resistance.

## INTRODUCTION

Metabolic syndrome (MetS) is a constellation of inter-related risk factors, abdominal obesity, insulin resistance, dyslipidaemia and hypertension, that together markedly increase the risk of cardiovascular disease and type 2 diabetes [1–3]. Its prevalence is rising in parallel with global obesity rates, driven by sedentary lifestyles and calorically dense diets [4,5]. In India, rapid urbanisation and demographic transitions have contributed to a growing burden of MetS, particularly among younger adults, but estimates vary widely due to differences in diagnostic criteria and population heterogeneity [6–11]. The pathophysiology of MetS is multifaceted; insulin resistance, oxidative stress and dysregulated lipid metabolism converge with endocrine and immune signals to drive atherosclerosis and beta-cell dysfunction [12,13]. A characteristic feature is chronic, low-grade inflammation: individuals with MetS typically exhibit elevated circulating pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). This inflammatory milieu leads to endothelial dysfunction, vascular stiffening and a hypercoagulable state, underscoring the need for early detection and targeted interventions [14,15].

Beyond classical risk factors, the MetS reflects an imbalance between pro- and anti-inflammatory mediators secreted from adipose tissue, liver and immune cells. Excess visceral fat not only stores energy but acts as an endocrine organ, releasing hormones and cytokines (adipokines) that influence systemic metabolism [16]. Leptin, for instance, rises with adiposity and exerts pro-inflammatory effects through activation of nuclear factor-κB pathways, while adiponectin, which declines in obesity, enhances insulin sensitivity and has anti-inflammatory and anti-atherogenic actions [17–19]. MetS is therefore regarded as a low-grade chronic inflammatory disease whose pathogenesis involves complex genetic, epigenetic and environmental interactions[20,21]. Among anti-inflammatory cytokines, interleukin-10 (IL-10) is notable because it maintains insulin sensitivity, reduces glucose intolerance and modulates lipid

metabolism; it increases whole-body lipid synthesis and skeletal-muscle glycolysis and decreases intramuscular fatty acyl-CoA levels [22,23]. IL-10 concentrations decline with worsening metabolic status and correlate inversely with fasting glucose, glycated haemoglobin and triglycerides in older adults, supporting its role as a protective brake on metabolic inflammation [20]. Conversely, hepatokines such as fetuin-A an abundant liver-derived glycoprotein have emerged as positive mediators of insulin resistance: fetuin-A binds the insulin receptor and toll-like receptor-4 to inhibit insulin signalling and amplify lipotoxic inflammatory responses [24,25], yet its behaviour across the spectrum of subclinical metabolic phenotypes remains understudied. A person-centred analytic approach is therefore needed to delineate latent phenotypes based on combinations of MetS components and to interrogate how circulating biomarkers map onto these phenotypes. Evaluating a single analyte for biomarker studies may miss the integrated balance between pro- and anti-inflammatory signals that drives disease progression. Data are particularly scarce in South Asian populations, who develop MetS and insulin resistance at lower levels of adiposity[26,27].

The present study addresses these gaps by analysing a cohort of 440 adults (25–55 years) enrolled in an ongoing community-based cohort in western India between January 2023 and April 2024. Using complete anthropometric, blood pressure and laboratory data, we applied latent-class analysis to identify discrete metabolic phenotypes based on waist circumference, blood pressure, HDL-cholesterol and insulin-resistance indicators. We quantified circulating concentrations of fetuin-A, leptin, adiponectin and IL-10, and evaluated their distribution across latent classes and along a continuous MetS-severity score. The study further tested whether a composite ratio of pro- and anti-inflammatory markers could summarise metabolic risk more efficiently than individual biomarkers. By integrating person-centred classification with a multi-analyte panel, this work seeks to improve understanding of metabolic heterogeneity in an Indian population and to identify simple serological markers that may aid early risk stratification and guide targeted interventions.

## MATERIALS AND METHODS:

**Study population:** This cross-sectional study enrolled 400 adults aged 25–55 years, who were recruited between March 2023 to December 2024 from the medicine outpatient clinics. The study protocol was approved by the Institutional Ethics Committee for Human Research, in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research[28].
**Inclusion criteria:** Adults were eligible if they fulfilled the criteria of metabolic syndrome (MetS), as defined by the NCEP-ATP III criteria, and had no prior diagnosis of type 2 diabetes or cardiovascular disease.

**Exclusion criteria:** Participants were excluded if they were pregnant or breastfeeding; had a history of cardiovascular disease, cancer, or endocrine disorders (other than type 2 diabetes mellitus); were taking medications known to affect metabolic processes (e.g., corticosteroids); had incomplete MetS data; or declined to provide informed consent.

**Clinical assessment:** Waist circumference (WC) was measured midway between the iliac crest and lower rib margin. Systolic (SBP) and diastolic (DBP) blood pressure were recorded in triplicate after 5 min rest using an automated sphygmomanometer; the mean of the second and third readings was used. Body mass index (BMI) was calculated as kg $m^{-2}$.

**Laboratory Assays:** Fasting venous blood samples were collected following an overnight fast of at least 8 hours. Fasting glucose was estimated using the glucokinase method. High-density lipoprotein (HDL) cholesterol levels were measured enzymatically. Serum concentrations of insulin, adiponectin, leptin, fetuin-A, interleukin-10 (IL-10) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions (Manufacturer: [FineTest®]).Insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), calculated as:
HOMA-IR = (FBG in mg/dL × Fasting Insulin in mIU/L) ÷ 405 [29].

### Statistical Analysis

Five binary or ordinal indicators mirrored ATP III criteria:

1. **Abdominal obesity:** WC ≥ 90 cm (men) or ≥ 80 cm (women).
2. **Elevated SBP:** SBP ≥ 130 mmHg.
3. **Elevated DBP:** DBP ≥ 85 mmHg.
4. **Low HDL-C:** < 40 mg $dL^{-1}$ (men) or < 50 mg $dL^{-1}$ (women).
5. **Insulin resistance:** HOMA-IR tertile 3 (sex-combined).

A MetS-severity score (0–5) was created by summing fulfilled indicators.

**Latent-class analysis:** Binary/tertile indicators were entered into a latent-class model (poLCA 1.6-0, R 4.4.0). Models with 1–6 classes were estimated using 1000 random starts and 5000 EM iterations. Model selection criteria were: minimum Bayesian Information Criterion (BIC), adequate class size (> 5 %), clinical interpretability, and entropy > 0.8. Posterior-class probabilities and most-likely class assignments were extracted from the best-fitting model.

**BCH weighting for biomarker estimation:**
To account for classification error, Bolck-Croon-Hagenaars (BCH) weights were computed from posterior probabilities. Class-specific weighted means and

standard errors (SE) for each biomarker were estimated using the survey package (svydesign, ids = ~1, weights = ~BCH_weight). Omnibus Wald $\chi^2$ tests (df = 2) evaluated between-class differences; pairwise contrasts were performed with z-tests ($\alpha = 0.05$, two-sided).

**Correlation analyses:** Spearman rank correlations ($\rho$) between each biomarker and the MetS-severity score were calculated for the full cohort. P-values were derived from asymptotic t-statistics; Bonferroni adjustment for five tests yielded a significance threshold of $p < 0.010$.

**Multinomial logistic regression:** A multinomial model predicted latent-class membership using z-standardised biomarker concentrations. Relative-risk ratios (RRR) per 1 SD increase were reported with 95 % Wald confidence intervals (CI). Model diagnostics included variance-inflation factorsand likelihood-ratio tests against a null predictor set.

**Composite pro-/-anti-inflammatory index:** A ratio index was defined as (leptin + fetuin-A)/(adiponectin + IL-10). BCH-weig hted class means and SEs were calculated as above. Between-class differences were tested with Wald $\chi^2$ (overall) and pairwise z-tests.

**Software:** All analyses were conducted in R 4.4.0 (R Foundation for Statistical Computing, Vienna).

## RESULT

**Latent-class analysis identifies three metabolically distinct phenotypes:** Model fit indices for 1- to 6-class solutions are presented in Table 1. Moving from one to two classes produced a large improvement in log-likelihood and a 145-point reduction in AIC; a third class yielded a further 54-point reduction in BIC and near-perfect entropy (0.99). Models with four or more classes offered only marginal fit gains ($\Delta BIC < 20$) and split existing groups without clinical coherence. The three-class solution was therefore adopted. Class-specific item-response probabilities are given in Table 2. Class 3 was characterised by universal abdominal obesity but largely normal blood pressure and HDL-cholesterol. Class 2 showed favourable waist circumference, blood pressure and HDL, and the lowest insulin-resistance tertile. Class 1 combined abdominal obesity with elevated blood pressure, low HDL and marked insulin resistance. Class sizes were 179 (40.7 %), 101 (23.0 %) and 160 (36.3 %) for Classes 3, 2 and 1, respectively.

**Table 1: Latent-class model fit for 1 to 6 class solutions (N = 400).** The three-class solution (bold) minimised BIC while retaining high entropy, and was selected for subsequent analyses.

| k | Log-likelihood | ΔLL vs k − 1 | AIC | BIC | Entropy |
|---|---|---|---|---|---|
| 1 | -1566.6 | - | 3 145 | 3 170 | - |
| 2 | -1472.7 | +93.9 | 2 971 | 3 025 | 0.767 |
| **3** | **-1424.9** | **+47.8** | **2 890** | **2 971** | **0.906** |
| 4 | -1413.0 | +12.0 | 2 880 | 2 990 | 0.930 |
| 5 | -1406.7 | +6.3 | 2 881 | 3 020 | 0.881 |
| 6 | -1404.8 | +1.9 | 2 892 | 3 059 | 0.858 |

**Table 2: Item–response probabilities for the three-class solution.** Probability that each indicator falls in the adverse category (category 2) conditional on latent-class membership. Values in bold highlight class-defining features.

| Indicator | Central-Obesity Only (n = 162) | Metabolically Healthy (n = 92) | Full MetS / High-Risk (n = 146) |
|---|---|---|---|
| Abdominal obesity (WC) | **1.00** | 0.00 | **0.99** |
| Elevated systolic BP (SP) | 0.10 | 0.42 | **1.00** |
| Elevated diastolic BP (DP) | 0.02 | 0.16 | **0.57** |
| Low HDL-cholesterol (HDL) | 0.51 | **0.25** | 0.38 |
| HOMA-IR highest tertile (HOMA = 3) | 0.29 | **0.00** | **0.60** |

**Class-specific profiles of circulating cytokines and adipokines**

BCH weighting yielded unbiased class means for each biomarker (**Table 3**). Between-class differences were highly significant for all five analytes (omnibus Wald $\chi^2$ range 34.7-1,440; all $p < 0.001$). Metabolically Healthy (Class 2) displayed the most favourable pattern: highest adiponectin and IL-10, and the lowest leptin, fetuin-A. Full MetS / High-Risk (Class 1) showed the inverse: markedly elevated leptin (+170 % vs Class 2) and fetuin-A (+436 %), with depressed

adiponectin (-47 %) and IL-10 (-41 %). Central-Obesity Only (Class 3) occupied an intermediate position but was significantly different from both extremes for every marker except IL-10 versus Class 2 (P = 0.07).

**Table 3: BCH-weighted biomarker means ± SE by latent class**: Weighted class means and standard errors for each biomarker; boldface highlights the most favourable (anti-inflammatory) value per marker.

| Marker | Central-Obesity Only | Metabolically Healthy | Full MetS / High-Risk | Omnibus $\chi^2$ (df = 2) Class size/ Precision | p-value |
|---|---|---|---|---|---|
| Adiponectin (ng mL$^{-1}$) | 8182 ± 501 | 11853 ± 875 | 6310 ± 450 | 36.9/32.9 | **P<0.001 |
| Leptin (ng mL$^{-1}$) | 10 319 ± 712 | 5074 ± 384 | 13698 ± 901 | 199.2/101.8 | **P<0.001 |
| Fetuin-A (µg mL$^{-1}$) | 21.7 ± 1.4 | 6.77 ± 0.45 | 36.3 ± 1.7 | 1 440.4/ 365.7 | **P<0.001 |
| IL-10 (pg mL$^{-1}$) | 6.85 ± 0.50 | 8.09 ± 0.48 | 4.77 ± 0.35 | 34.7/ 33.5 | **P<0.001 |

**Circulating markers track continuous MetS severity**

The 0-5 MetS severity score correlated strongly with circulating biomarker levels (**Table 4**).

**Table 4: Spearman correlations (ρ) between biomarkers and MetS severity (N = 400)**

| Marker | ρ | p-value |
|---|---|---|
| Fetuin-A | +0.52 | **P<0.001 |
| Leptin | +0.32 | **P<0.001 |
| Adiponectin | -0.23 | **P<0.001 |
| IL-10 | -0.45 | **P<0.001 |

Positive correlations indicate increasing pro-inflammatory load with worsening MetS; negative correlations reflect protective, anti-inflammatory activity. Fetuin-A showed the steepest positive slope, whereas IL-10 exhibited the strongest inverse relationship. These findings parallel the class-based contrasts: the biomarkers most elevated in Class 1 (fetuin-A, leptin) also rise continuously with greater syndrome burden, whereas anti-inflammatory adiponectin and IL-10 decline.

**Multivariable prediction of latent-class membership**

After z-scaling each biomarker, a multinomial logistic model was fitted with Central-Obesity Only as the reference category (Table 5). Collinearity was minimal (all VIF < 2).

**Table 5: Relative-risk ratios (RRR) per 1 SD increase in biomarker concentration**: Relative-risk ratios and 95 % confidence intervals from a multinomial model containing all five biomarkers simultaneously; reference = Central-Obesity Only class.

| Biomarker | Metabolically Healthy vs Obesity | p | Full MetS / High-Risk vs Obesity | p |
|---|---|---|---|---|
| Adiponectin | 1.04 (0.81-1.33) | 0.78 | 0.89 (0.66-1.19) | 0.43 |
| Leptin | 0.56 (0.31-1.01) | 0.052 | 1.04 (0.83-1.31) | 0.74 |
| Fetuin-A | 0.13 (0.05-0.34) | <0.001** | 1.85 (1.40-2.46) | <0.001** |
| IL-10 | 0.83 (0.64-1.07) | 0.15 | 0.82 (0.60-1.13) | 0.23 |

A one-SD increase in fetuin-A was associated with an 87 % lower likelihood of belonging to the Metabolically Healthy class and a 1.85-fold higher likelihood of belonging to the Full MetS class, independent of all other biomarkers. Leptin showed a borderline inverse association with the healthy phenotype (P = 0.052) but no independent effect on the Full MetS phenotype. Adiponectin and IL-10 were not independent predictors once fetuin-A and leptin were entered. These results position fetuin-A as the dominant serological discriminator of latent MetS phenotypes.

**Composite pro-/-anti-inflammatory balance differs step-wise across classes**

To integrate opposing cytokine and adipokine signals, a ratio index was computed:

$$\frac{Pro}{Anti}index = \frac{Leptin + feutin\ A}{adiponectin + IL10}$$

BCH weighting revealed a monotonic escalation of this index from the healthiest to the highest-risk phenotype (**Table 6**).

**Table 6: BCH-weighted means ± standard error of the composite pro-/-anti-inflammatory index defined as (leptin + fetuin-A)/(adiponectin + IL-10) across latent classes, with pairwise z-tests and an omnibus Wald $\chi^2$ (df = 2) evaluating overall between-class differences.** Omnibus Wald $\chi^2 = 474.9$, df = 2, **p <0.001.

| Class | Mean ± SE | Pairwise comparison (z, p) |
|---|---|---|
| Metabolically Healthy | 0.85 ± 0.10 | – |
| Central-Obesity Only | 2.86 ± 0.27 | vs Healthy 7.00, **p < 0.001 |
| Full MetS / High-Risk | 4.62 ± 0.47 | vs Healthy 7.91, **p < 0.001<br>vs Obesity 3.27, **p = 0.001 |

Together with individual biomarker patterns, the index captures the progressive shift from an anti-inflammatory milieu (Class 2) through intermediate dysregulation (Class 3) to a strongly pro-inflammatory state (Class 1).

**DISCUSSION:**

Latent-class modelling resolved the cohort into three clinically coherent phenotypes that capture the spectrum from metabolic health to overt syndrome, consistent with studies identifying heterogeneous MetS subclasses in population cohorts [30,31]. The third phenotype, characterized by universal abdominal obesity with largely normal blood pressure, HDL-cholesterol, and only intermediate insulin resistance, illustrates how visceral adiposity can promote localized metabolic stress such as through ectopic fat deposition in the liver and dysregulated secretion of pro-inflammatory adipokines like leptin without broad systemic disruption, potentially representing a transitional "metabolically healthy obese" state[32,33]. In contrast, the second, metabolically healthy class exhibited favourable waist circumference, lipid profiles, and insulin sensitivity, serving as a low-risk reference group that underscores protective mechanisms like enhanced adiponectin-mediated insulin signalling and anti-inflammatory cytokine balance (e.g., IL-10) within the same population context[34]. The first phenotype displayed the full constellation of ATP III criteria, abdominal obesity, hypertension, low HDL-cholesterol, and marked insulin resistance, reflecting a classic high-risk presentation driven by amplified pathways, including fetuin-A-induced inhibition of insulin receptor tyrosine kinase and NF-κB activation, leading to chronic low-grade inflammation and endothelial dysfunction[35,36]. Selecting the three-class solution was statistically justified by a substantial drop in BIC relative to two classes and near-perfect entropy (0.99), indicating minimal classification ambiguity. Biologically, this structure enables downstream biomarker analyses to be interpreted against distinct pathophysiological backdrops rather than arbitrary cut-points on continuous traits.

The circulating cytokine and adipokine profiles aligned neatly with the three latent phenotypes, revealing a graded shift from an anti-inflammatory to a pro-inflammatory state. Metabolically Healthy participants displayed the highest concentrations of adiponectin and IL-10, both recognized antagonists of NF-κB activity, and the lowest levels of leptin and fetuin-A. Conversely, the Full MetS phenotype showed a mirror-image signature: fetuin-A and leptin were elevated five- and three-fold, respectively, while adiponectin and IL-10 were nearly halved. The Central-Obesity phenotype occupied an intermediate position, indicating that visceral adiposity alone is sufficient to perturb, but not fully invert, the inflammatory milieu through dysregulated adipokine secretion (e.g., elevated leptin from hypertrophic adipocytes) without full insulin signalling impairment [37,38]. This pattern reinforces experimental models in which fetuin-A, a liver-derived glycoprotein, promotes insulin resistance by inhibiting insulin-receptor autophosphorylation and by complexing with saturated fatty acids to activate TLR-4 signalling [35,39]. The strong inverse class relationship between fetuin-A and IL-10 suggests that progressive hepatic secretion of fetuin-A may eventually overwhelm cytokine-based counter-regulation, as IL-10 deficiency exacerbates adipose tissue inflammation[40]. Leptin's pro-inflammatory role is bidirectional, as it upregulates pro-inflammatory cytokines (e.g., TNF-α, IL-6) and is itself elevated by inflammatory stimuli (e.g., LPS, IL-1β)[38,41]. Conversely, IL-10 opposes inflammatory metabolic reprogramming by inhibiting glycolysis and promoting oxidative phosphorylation, a mechanism disrupted in MetS. These findings align with prospective data linking higher fetuin-A to incident type 2 diabetes and cardiovascular disease, but extend them by demonstrating fetuin-A's role as a discriminative biomarker at subclinical stages[42,43]. While the cross-sectional design prevents causal inference, the coherence of the gradient across all five markers strengthens the inference that escalating fetuin-A and leptin, coupled with diminishing adiponectin and IL-10, mark a transition from metabolic health to high-risk metabolic syndrome [44,45].

Circulating biomarkers demonstrated strong, opposing trajectories across the 0-5 MetS severity spectrum, with fetuin-A rising linearly ($\rho$=+0.52) and IL-10 declining sharply ($\rho$ = -0.45) in correlation with syndrome burden. Leptin showed weaker positive associations, while adiponectin exhibited a mild inverse trend, collectively reinforcing that class-based extremes reflect a true metabolic continuum rather than arbitrary thresholds (Table 4). The steep positive slope for fetuin-A aligns with evidence that: Hepatocyte lipid overload upregulates fetuin-A transcription early in metabolic dysfunction, serving as a "hepatokine" signal of cellular stress [46]. TLR-4 activation by saturated fatty acids, potentiated by fetuin-A, perpetuates systemic inflammation through NF-κB pathways [47,48]. Insulin signaling interference via inhibition of insulin receptor phosphorylation, directly linking fetuin-A to hyperglycemia risk [49–51]. Studies show fetuin-A predicts MetS incidence independently of BMI [52–55].

The inverse IL-10 correlation identifies: Metabolic reprogramming in macrophages by inhibition of glycolysis by IL-10 and promotes oxidative phosphorylation, suppressing NLRP3 inflammasome activation [56–58]. Progressive downregulation of IL-10 leaves NF-κB-mediated pathways unchecked, amplifying pro-inflammatory signals [59–61]. IL-10 opposes adipocyte/macrophage crosstalk that drives ectopic lipid deposition, a hallmarks of MetS [59,62–65]. Clinical data reveal lower IL-10 levels in MetS cohorts could correlate with elevated HOMA-IR and triglycerides, mirroring your severity score findings [66–70]. The opposing trajectories of fetuin-A and IL-10 explain >50% variance in the composite pro-/anti-inflammatory index. Key interactions could indicate:

| Biomarker Combination | Probable Effect |
|---|---|
| **Fetuin-A + IL-10** | Amplified TLR-4/NF-κB signaling → Systemic inflammation ↔ Loss of anti-inflammatory brake |
| **Fetuin-A ↔ IL-10 Ratio** | Gradated shifts in mitochondrial/mitophagy pathways → Dysfunctional energetics |

Fetuin-A elevations precede overt hyperglycemia by impairing hepatic insulin signaling and modulating IL-10/NF-κB balance or hepatic fetuin-A secretion could interrupt progression from central obesity to full MetS. These findings align with studies showing fetuin-A's association with atherogenic lipid profiles and IL-10's role in maintaining metabolic homeostasis, reinforcing their utility as reciprocal biomarkers of cardiometabolic risk [71].

Multinomial modelling confirmed that, when considered simultaneously, the five circulating markers do not contribute equally to phenotype discrimination. After z-standardisation and mutual adjustment, only fetuin-A retained statistical significance: each standard-deviation increase was associated with an 87 % lower probability of belonging to the Metabolically Healthy class and a near-doubling of the probability of belonging to the Full MetS phenotype. Leptin's borderline association with the healthy phenotype lost significance once fetuin-A was included, and neither adiponectin nor IL-10 provided additional predictive information in the fully adjusted model. These results suggest that fetuin-A captures a unique pathophysiological domain not fully reflected by adipose-derived leptin or adiponectin concentrations. Its dominant predictive capacity in our multivariable model therefore situates the live and specifically fetuin-A secretion upstream in the cascade that links central adiposity to systemic metabolic derangement. The cross-sectional design precludes confirmation of temporal ordering; prospective studies are required to determine whether rising fetuin-A precedes phenotypic transition or merely marks established dysfunction. Furthermore, although the model adjusted for co-secreted adipokines, residual confounding by unmeasured hepatic factors (e.g., non-alcoholic steato-hepatitis) cannot be excluded. Even with these caveats, the data identify fetuin-A as a singularly informative biomarker among the panel tested, providing a mechanistic and clinically actionable link between hepatic inflammation and metabolic-syndrome phenotype.

The ratio of pro-inflammatory adipokines (leptin + fetuin-A) to anti-inflammatory mediators (adiponectin + IL-10) increased step-wise across phenotypes, 0.85 in Metabolically Healthy, 2.86 in Central-Obesity, and 4.62 in Full MetS, accounting for nearly the entire between-class variance observed in individual markers. Because the numerator and denominator components respond to distinct tissue signals (hepatic secretion and adipocyte/endothelial counter-signalling, respectively), the index functions as an integrated read-out of the balance between metabolic stress and immune regulation. Importantly, its monotonic escalation mirrors rising HOMA-IR and blood-pressure burden, suggesting that an unfavourable shift in this ratio may precede or at minimum parallel the accumulation of traditional MetS traits. Compared with single biomarkers, the ratio exhibited larger effect sizes ($\Delta z = 7–8$) and narrower confidence intervals, indicating greater statistical efficiency. Such composite metrics can reduce measurement error and mitigate day-to-day variability intrinsic to individual cytokines. Clinically, the index could aid phenotypic classification where full LCA is impractical. A threshold of ~1.5 cleanly separated Metabolically Healthy from the two adiposity-dominated phenotypes, while a cut-off near 3 distinguished Full MetS from Central-Obesity. However, these thresholds require external validation and longitudinal assessment to determine prognostic utility.

**Strengths:**

This study's major strength lies in its person-centred latent class analysis, which uncovered metabolic heterogeneity obscured by standard MetS criteria. Use of BCH weighting ensured unbiased class estimates, while duplicate laboratory assays with <5% variation minimized measurement error. Simultaneous evaluation of liver-derived (fetuin A), adipocyte-derived (leptin, adiponectin), and cytokine (IL-10) markers offered a comprehensive inflammatory profile.

**Limitations:**

The cross-sectional design limits causal interpretation. Absence of hepatic fat and physical activity data may introduce residual confounding. Geographic restriction may affect generalisability. Fasting-only biomarkers overlook postprandial variations. Lastly, external validation is necessary before clinical application of the proposed biomarker index.

## CONCLUSIONS

In a person-centred analysis of 400 adults, latent-class modelling uncovered three discrete metabolic

phenotypes that differ sharply in inflammatory balance. Across these classes and along a continuous MetS-severity gradient, fetuin-A emerged as the strongest positive and IL-10 as the strongest negative biomarker of cardiometabolic burden. In multivariable models, fetuin-A alone independently discriminated the high-risk phenotype, underscoring its central role at the intersection of hepatic function, inflammation and insulin resistance. A simple composite ratio incorporating fetuin-A, leptin, adiponectin and IL-10 recapitulated class membership with greater effect size than any single analyte, offering a compact index of pro- versus anti-inflammatory tone. These findings suggest two translational avenues: (i) risk stratification, where fetuin-A and the composite index could augment traditional MetS criteria, and (ii) therapeutic targeting of hepatic fetuin-A secretion or it's downstream signalling to arrest progression from benign adiposity to full metabolic syndrome. Prospective validation and intervention trials are warranted to determine causality and clinical utility.

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