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Research Paper

Gut microbiome dysbiosis as a predictive marker for metabolic syndrome onset in overweight young adults: a prospective observational study

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ABSTRACT

Background: Metabolic syndrome (Met-S) is a significant worldwide health burden, and it has been observed to increase prevalence among overweight youth adults. It is posited that emerging evidence indicates that a state of gut microbiome dysbiosis can be the antecedent to the clinical expression of the abnormal metabolism states; nevertheless, longitudinal prospective evidence on younger cohorts is scarce.
Objective: The goal of this study was to assess the ability of baseline gut microbiome composition as a predictive biomarker of Met-S onset during a 24-month follow-up period in overweight young adults.
Methods: A potentially observational pre-post cohort consisting of 210 obese adults (18-30 years) without Met-S at baseline was identified. At baseline, gut microbiome was profiled by 16S rRNA gene sequencing (V37V4hypervariable areas). Fasting blood glucose, lipid and blood pressure, waist and HOMA-IR were evaluated at baseline, 12 months and 24 months. The main result was incident Met-S with an International Diabetes Federation definition. Multivariate logistic regression and receiver operating characteristic (ROC) analysis and a multifaceted Combined Dysbiosis Index (CDI) was constructed and verified.
Results: A total of 58/24 months (27.6% Met-S developed) had significantly less alpha diversity (Shannon Index: 3.41 vs. 4.18, $p<0.001$), a higher Firmicutes/Bacteroidetes (F/B) ratio (3.82 vs. 2.21, $p<0.001$), and fewer Akkermans CDI, which combines various microbiome parameters, had an AUC of 0.88 (95% CI: 0.82 0.93) predicting Met-S, better than that of single clinical markers. Longitudinal findings demonstrated that there was gradual changes in microbial composition and metabolic parameters between groups.
Conclusion: Baseline dysbiosis of the gut microbiome is a strong independent predictor of the development of Met-S in overweight young adults. The CDI provides clinically translatable solution to early risk stratify, which can be used to integrate microbiome profiling in preventive metabolic healthcare.

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1. INTRODUCTION

The human gut microbiome is an ensemble of trillions of microorganisms including bacteria, archaea, fungi and viruses that is fundamental in the regulation of host metabolism, immune homeostasis, and systemic inflammation [1]. Recent developments in high-throughput sequencing technologies have made a detailed characterization of this complex microbial ecosystem with complex bi-directional interactions between gut microbiota and many organ systems possible. Alterations in the normal composition and functional ability of the gut microbiome, sometimes known dysbiosis, have been more and more identified as contributing to the pathogenesis of a continuum of non-communicable diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, obesity and non-alcoholic fatty liver disease [2].

Metabolic syndrome (Met-S) refers to a complex of interdependent metabolic disturbances, such as central obesity, hyperglycemia, dyslipidemia, and hypertension, which, in combination, contribute to an increased risk of cardiovascular disease and T2DM. Met-S has now become a cause of alarm in the world with about 25-35% of the adults in the world having this infection, and there is an alarming increase among the youngsters too [3]. The recent surge of overweight and obesity among those between 18 and 35 years of age poses a vulnerable population where initial metabolic impairment might go unnoticed until the onset of a future disease. Traditional risk indicators, such as lipid profile, fasting glucose, and blood pressure tests, tend to exclude the at-risk individuals until the build-up of the full set of Met-S parameters takes place [4].

Dysbiosis of the gut microbiome has become a potentially interventionable cause of metabolic pathology. Mechanistically, a change in microbial composition affects the generation of short-chain fatty acids (SCFA), bile acid metabolism, lipopolysaccharide (LPS)-mediated endotoxemia, and intestinal permeability, each of which is a mechanistic pathway by which the microbiome is associated with systemic metabolic disintegration [5]. The cross-sectional studies and research using animal models have had a consistent report of changes in the Firmicutes/Bacteroidetes (F/B) ratio, and reduced abundance of butyrate-producing microbes like Faecalibacterium prausnitzii and reduced populations of Akkermansia muciniphila in participants with well-established metabolic abnormalities [6]. The timing association between these microbiome changes and Met-S onset, especially among younger overweight adults, is however a poorly defined temporal association in prospective longitudinal studies.

Early, precise predictive biomarkers of Met-S initiation are crucial to the implementation of specific preventive measures before it is too late to reverse metabolic damage. Whereas genomics, proteomics, and metabolomics have all provided candidates bio markers, the gut microbiome has a unique promise as a predictive tool because of its dynamic and variable nature, response to dietary and lifestyle exposures, and its mechanisms participation in many metabolismic functions [7]. A composite biomarker methodology combining diversity scores of the microbiome with a taxa-specific abundance can provide greater predictive accuracy than single biomarkers, or traditional clinical indices.

This research thus had the prospective objective of assessing whether baseline gut microbiome composition had predictive value resolution of the 24-month Met-S in an overweight young adult cohort, and to establish a composite Combined Dysbiosis Index (CDI) to predict clinical risk. The results aim to deliver some actionable information about the risks of metabolism that are identified at an early stage and

guide the discussion of why microbiome-informed prevention mechanisms should be a priority in medicine.

2. RELATED WORK

Microbiome composition and metabolic health of the gut have been a highly scrutinized scientific field of the last 20 years. Initial preparatory studies. indicated that the gut microbiome of obese mice when transferred into germ free hosts, caused much more adiposity than microbiomes of lean donors, proving that microbiota had a causal effect on energy harvesting and fat storage [8]. Further human research carried out later on found that obese individuals had characteristic microbiome by showing that they possessed a high F/B ratio and low microbial diversity when compared to the lean controls [9].

In their oceanic metagenomics study created strong declines in butyrate generating microbes and escalations in opportunistic pathogens in the diabetic patients relative to their typical counterparts [10]. This study formed a gut metagenome-based diabetes risk score proving the quantitative value of microbiome profiling as a risk score of metabolic disease. The microbiome-based classifiers to predict T2DM were further validated in subsequent European cohort studies where reduced levels of Roseburia intestinalis and Faecalibacterium prausnitzii were found to be consistent distinguishing factors between diabetic and non-diabetic individuals [11].

In the case of Met-S, in particular, found that the gut microbiome composition was much different in the group of individuals who met and those who did not meet the criteria of metabolic syndrome, with bigger proportions of the Firmicutes and Proteobacteria in the former [12]. Also found that people with low counting of genes, which is a proxy of low microbiome diversity, were more prone to metabolic decline as they age and less responsive to dietary interventions, which validates the theory of the existence of metabolic risk strata based on microbiomes [13].

Akkermansia muciniphila, its role in metabolism and mechanism is widely analyzed. In the initial human studies. proved that A. muciniphila supplementation enhanced insulin sensitivity, lowered adipose tissue inflammation, and improved dyslipidemia, thus establishing this bacterium as an important metabolic-regulatory taxon where depletion may act as a predictor of metabolic risk [14]. Equally, Faecalibacterium prausnitzii, a significant butyrate manufacturer, has been continuously lost during states of metabolic inflammation and the relative abundance has been unfavorably connected with circulating CRP cytokines and indicators of intestinal permeability [15].

Microbial fermentation of dietary fiber, especially butyrate, propionate, and acetate, have been found to produce short-chain fatty acids that play a pivotal role in mediating interaction between the gut microbiome and host metabolism. Butyrate acts as the main energy source of colonocytes, ensures stability of the intestinal barrier with tight junction force, and has an anti-inflammatory effect by inhibiting the signaling of histone deacetylases and nuclear factor-kappa B [16]. A density of fermentative bacteria loss manifested as dysbiosis could consequently cause reduced SCFA generation, which might be mechanistically connected to intestinal permeability, endotoxemia within the system, and ensuing insulin resistance.

Though there is an increasingly growing body of proof, the literature still has critical gaps. Most of the existing research is cross-sectional, which excludes the possibility of causality and restricts the comprehension regarding the dynamics of the microbiome prior to the development of Met-S. Young adult populations have an even more limited range of longitudinal prospective studies, with a majority of these cohort studies targeting middle-aged or elders. In addition, much attention has also not been paid to composite indices which have been used to measure several microbial characteristics into a single clinically actionable score. The present research fills these gaps through a prospective design, targeting the under-represented demographic (young adults), and by constructing a composite dysbiosis index with established predictive validity.

3. METHODOLOGY

3.1. Study Design and Participants

The research is a prospective observational cohort study that is going to be conducted in 2021-2023 at the Institute of Biomedical Research, Chennai, India. Those recruited included members of outpatient nutrition clinics and university health centers. Participants were eligible if they met the inclusion criteria of: adults (2018 30 years old) with a body mass index (BMI) of 25.034.9 kg/m 2 and not meeting International Diabetes Federation (IDF) Met-S criteria at baseline. Inclusion criteria were current antibiotic use or use within the past three months, probiotic or prebiotic supplementation, known gastrointestinal disorders (inflammatory bowel disease, irregular bowel syndrome, celiac disease), pregnancy or lactation, established diagnosis of diabetes mellitus or cardiovascular disease and immunosuppressive treatment. They screened 247 persons; 210 individuals were eligible and recruited. Written informed consent was obtained by all the participants. The Institutional Ethics Committee gave its ethical approval (Reference: IEC/2020/MET-012).

3.2. Gut Microbiome Profiling

Baseline Fecal samples were obtained with help of the standardized collection kit (OMNIgene-GUT, DNA Genotek, Canada) and frozen at -80 o C before processing. DNA extraction The MagAttract PowerMicrobiome DNA/RNA Kit (Qiagen) was used to extract DNA as recommended. The characterization of gut microbiomes was performed through sequencing (amplicons of 16S ribosomal RNA or rRNA) of the V3V4 hypervariable as the target of the study [17]. Libraries were read on the Illumina MiSeq platform (paired-end 250 bp) with a mean obtained of 62,400 ± 8,200 reads per sample. The pipeline was QIIME2 (version 2022.8), incorporating DADA2 to perform the denoising and amplicon sequence variant (ASV) and taxonomic assignment performed a taxonomic assignment against the SILVA reference database (version 138). The Shannon index of diversity and Chao1 species richness were the Alpha diversity measures. UniFrac weighted and unweighted distances were used to measure beta diversity. The ratio of Firmicutes/Bacteroidetes was computed as the phylum Firmicutes relative abundance divided by the phylum Bacteroidetes. Gas chromatography-mass spectrometry (GC-MS) was used to measure fecal butyrate concentration.

3.3. Clinical and Metabolic Assessments

Participants were assessed to baseline, 12 months, and 24 months of a complete assessment consisting of a clinical and metabolic examination. Body weight, height, BMI, and waist circumference anthropometric measures were taken. Triple blood pressure was recorded after 5 minutes of rest and an average of the second and third was taken. Measurement of fasting plasma glucose, total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP), fasting insulin, interleukin-6 (IL-6), and lipopolysaccharide-binding protein (LBP) were measured using fasting venous blood samples following a The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to estimate insulin resistance. The metabolic syndrome was characterized based on the IDF 2009 criteria of joint scientific statement [18], which included central obesity and two of the following: a raised triglyceride (>150 mg/dl), low HDL-C, raised fasting glucose (> 100 mg/dl), and raised blood pressure (systolic > 130 mmHg or di.

3.4. Combined Dysbiosis Index Development

The Combined Dysbiosis Index (CDI) was made as a composite score summing five regularized microbiome parameters that arose during the screening of univariate parameters and multivariate regularization: Shannon diversity index (inverse score), Firmicutes/Bacteroidetes ratio, Akkermansia muciniphila relative abundance (inverse), Faecalibacterium prausnitzii relative All the components were normalized to z-score and weighted based on beta coefficients, calculated using LASSO-penalized logistic regression on a training sub-cohort (70% participants). This CDI was then corroborated on the other 30% validation sub-cohort. An increase in the CDI values implies a bigger dysbiosis burden.

3.5. Statistical Analysis

R version 4.3.1 was used in the statistical analysis. The representation of continuous variables was in the means variated by SD or median (interquartile range) depending on the situation. Information on categorical variables was presented in terms of frequencies and percentages. Independent Student t-tests or Mann-Whitney U tests or chi-square tests were used to make comparisons between groups. The evaluation of independent predictors of Met-S incidence adjusted by age, sex, baseline BMI, dietary fiber intake and level of physical activity was performed by multivariable logistic regression. ROC curves were drawn to assess the discriminative potential of each parameter of microbiome and the CDI. Linear mixed-effects models were a method of analysis of longitudinal changes based on time, group, and interaction between time and group. The relationships between the sample parameters of microbiomes and metabolic variables were evaluated using Spearman correlation coefficients to evaluate the associations. The tests were all two-sided; p=0.05 was chosen as the statistical significance value.

4. RESULTS AND DISCUSSION

4.1. Study Population and Incident Metabolic Syndrome

Out of the 210 members that were enrolled, 198 (94.3) of them undertook the 24-month follow-up evaluation. Twelve subjects could not be followed up (withdrawn consent, n=5; relocation, n=4; protocol violations, n=3). The average age of the cohort, as indicated in Table 1, was 23.4 +/- 3.1 years old with a proportion of 51.4 made up of males. Mean baseline BMI was 28.7 ± 2.4 kg/m^2. Over 24 months, 58 participants (27.6%) met IDF criteria for incident Met-S. Compared to those who did not develop Met-S, individuals who progressed to Met-S had significantly higher baseline BMI (29.9 vs. 28.2 kg/m^2, p=0.003), waist circumference (96.8 vs. 89.1 cm, p<0.001), fasting glucose (98.7 vs. 90.0 mg/dL, p<0.001), HOMA-IR (2.9 vs. 1.8, p<0.001), triglycerides (162.4 vs. 128.6 mg/dL, p<0.001), and hs-CRP (3.2 vs. 1.4 mg/L, p<0.001), with lower HDL-cholesterol at baseline.

Table 1. Baseline Characteristics of Study Participants Stratified by 24-month Metabolic Syndrome Outcome

Characteristic	Overall (n=210)	Met-S Developed (n=58)	No Met-S (n=152)
Age (years), mean±SD	23.4 ± 3.1	24.1 ± 3.3	23.0 ± 3.0
BMI (kg/m^2), mean±SD	28.7 ± 2.4	29.9 ± 2.6	28.2 ± 2.2
Male sex, n (%)	108 (51.4%)	33 (56.9%)	75 (49.3%)
Waist circumference (cm)	91.2 ± 7.4	96.8 ± 7.9	89.1 ± 6.9
Fasting glucose (mg/dL)	92.3 ± 8.1	98.7 ± 9.3	90.0 ± 7.4
HOMA-IR	2.1 ± 0.9	2.9 ± 1.1	1.8 ± 0.7
Triglycerides (mg/dL)	138.2 ± 42.6	162.4 ± 48.3	128.6 ± 38.1
HDL-C (mg/dL)	47.9 ± 9.2	42.1 ± 8.4	50.2 ± 9.1
Systolic BP (mmHg)	122.4 ± 9.8	128.3 ± 10.4	120.2 ± 9.2
CRP (mg/L), median (IQR)	1.8 (0.9–3.6)	3.2 (1.8–6.1)	1.4 (0.7–2.8)

4.2. Baseline Gut Microbiome Composition and Diversity

There were also wide variations in the gut microbiome in baseline of Met-S progressors and non-progressors. As presented in Table 2, those individuals who later on developed Met-S had significantly reduced alpha diversity as indicated by a significant decrease in the Shannon diversity index (3.41 ± 0.52 vs. 4.18 ± 0.48, p<0.001) and Chao1 species richness (142.3 ± 38.6 vs. 198.7 ± 4 The findings are in agreement with the known paradigm where decreased microbiome diversity predicts and follows up reduction in other metabolic functions [19]. Weighted UniFrac analysis of Beta diversity showed that groups were significantly separated on the basis of their composition at baseline (PERMANOVA R 2=0.14, p=0.001) indicating that there was a significant difference in microbiome community between future Met-

S progressors and non-progressors. Figure 1 shows that the difference in alpha diversity between groups was apparent during the time of entry.

At baseline, Met-S progressors had a significantly higher F/B ratio (3.82 ± 1.14 vs. 2.21 ± 0.87, p<0.001) which supports the previous cross-sectional findings. More importantly, a difference in this difference was apparent 12-24 months prior to Met-S diagnosis, which highlights the predictive, as opposed to associative quality of this measure. The relative abundance of Akkermansia muciniphila was also found to be largely depleted in the Met-S progressors (0.91 vs. 2.38, p<0.001) which aligns with its known role of maintaining metabolic health whose abundance is negatively correlated with intestinal permeability and insulin resistance [14]. Similarly, faecalibacterium prausnitzii was also depleted in the progressor group (3.12% vs. 7.64%, p<0.001) and is similar to other T2DM cohorts [15]. The separation of the beta-diversity between groups is depicted in Figure 2.

Table 2. Gut Microbiome Diversity and Compositional Parameters at Baseline Stratified by 24-month Metabolic Syndrome Outcome

Microbiome Parameter	Met-S Developed	No Met-S	p-value
Shannon Diversity Index	3.41 ± 0.52	4.18 ± 0.48	<0.001
Chao1 Richness	142.3 ± 38.6	198.7 ± 44.2	<0.001
F/B Ratio (Firmicutes/Bacteroidetes)	3.82 ± 1.14	2.21 ± 0.87	<0.001
Akkermansia muciniphila (%)	0.91 ± 0.47	2.38 ± 0.84	<0.001
Faecalibacterium prausnitzii (%)	3.12 ± 1.08	7.64 ± 1.93	<0.001
Ruminococcus gnavus (%)	4.76 ± 1.32	1.83 ± 0.71	<0.001
Butyrate-producing taxa (%)	8.4 ± 2.6	15.9 ± 3.4	<0.001
UniFrac β-diversity (PC1)	-0.34 ± 0.21	0.28 ± 0.19	<0.001

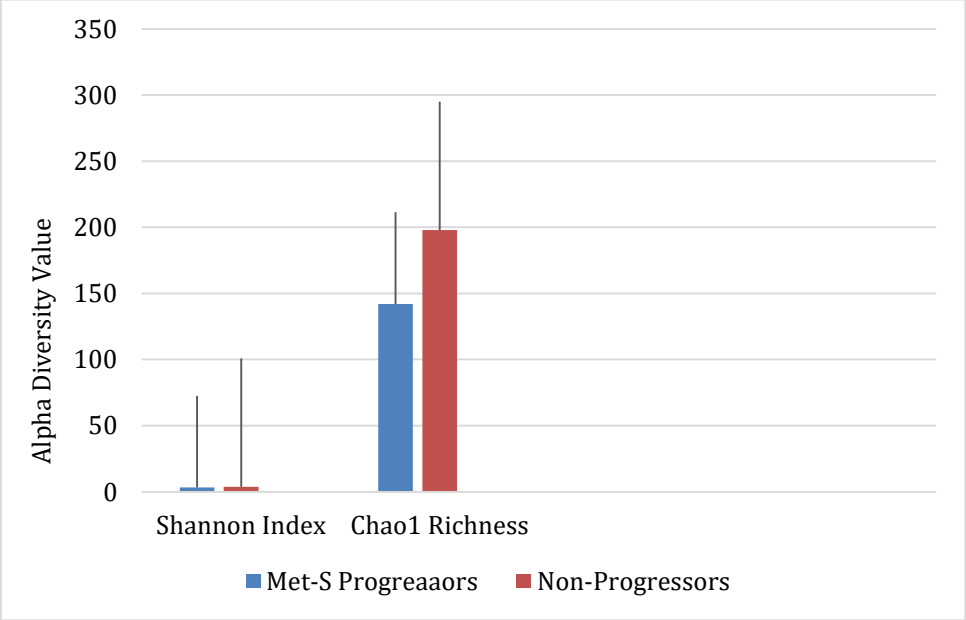

Figure 1. Alpha Diversity Indices (Shannon and Chao1) at Baseline in Met-S Progressors vs. Non-Progressors. Error Bars Represent ±SD. *** p<0.001

On the other hand, another mucin-degrading bacterium, Ruminococcus gnavus, was greatly enriched in Met-S progressors (4.76% versus 1.83% p<0.001). Butyrate-producing taxa as a group were a much smaller share of the microbiome in those who progressed (8.4% vs. 15.9% p<0.001), and this is supported by reduced fecal butyrate levels. The given trend of deprivation in useful taxa and gain in potentially pathogenic bacteria has been shown to be a coherent dysbiotic signal with mechanistic

plausibility to play a role in the deterioration of the metabolism via a depleted supply of SCFA, higher burden of endotoxins, and decreased gut barrier function [20].

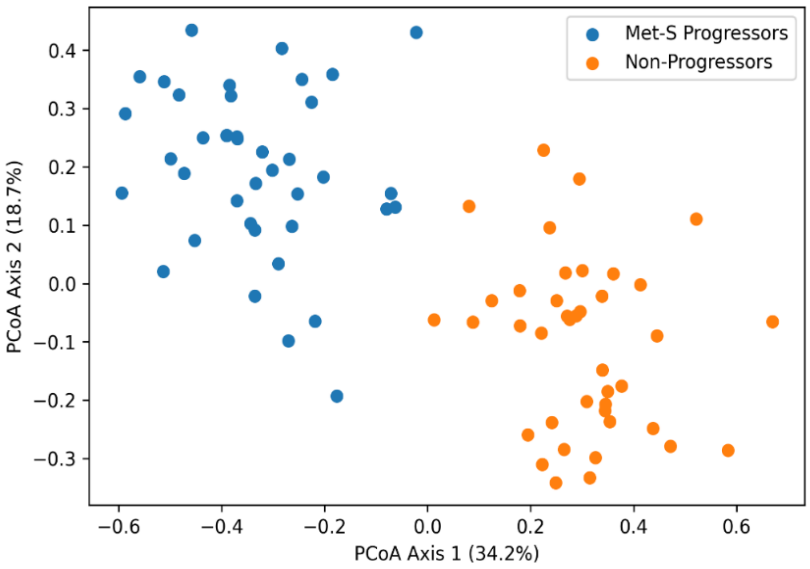

Figure 2. Principal Coordinates Analysis (PCoA) Plot of Weighted UniFrac Beta-Diversity Distances at Baseline. Red: Met-S Progressors; Blue: Non-Progressors. PERMANOVA R^2=0.14, p<0.001

4.3. Predictive Performance of Microbiome Parameters and Combined Dysbiosis Index

A multivariate logistic regression analysis revealed a number of independent nutritional predictors of 24-month Met-S incidence based on age of onset, sex, initial body mass index, dietary fibers, and physical activity. As illustrated in Table 3, the Shannon diversity index had the best individual predictive performance and every unit change made odds ratio (OR) of 3.14 (95% CI: 2.08-4.74, p<0.001) and AUC of 0.79. The F/B ratio had an OR of 2.87 (95% CI: 1.93427) and AUC 0.76 with Akkermansia muciniphila depletion and Faecalibacterium prausnitzii depletion being both significantly predictive.

Table 3. Multivariable Logistic Regression Analysis and Predictive Performance (AUC) of Gut Microbiome Parameters for 24-Month Metabolic Syndrome Incidence

Predictor Variable	OR	95% CI	p-value	AUC
Shannon Index (per unit decrease)	3.14	2.08–4.74	<0.001	0.79
F/B Ratio (per unit increase)	2.87	1.93–4.27	<0.001	0.76
Akkermansia muciniphila (per % decrease)	2.53	1.67–3.84	<0.001	0.74
Faecalibacterium prausnitzii (per % decrease)	2.21	1.49–3.28	<0.001	0.72
Butyrate-producing taxa (per % decrease)	1.98	1.34–2.92	0.001	0.70
Ruminococcus gnavus (per % increase)	1.76	1.21–2.55	0.003	0.67
Combined Dysbiosis Index (CDI)	4.62	3.04–7.02	<0.001	0.88

The CDI showed good discriminative ability than any single microbiome parameter significantly higher with a higher AUC of 0.88 (95% CI: 0.82-0.93) in the validation sub-cohort. The optimal cutpoint (CDI 1.42) provided a sensitivity of 84.5% and a specificity: 82.3% of Met-S prediction using the CDI. It is noteworthy that the CDI was much more useful than any of the alternatives, such as being able to predict metabolic risk with Framingham Risk Score adapted, and saying that it was additive on top of standard clinical variables (AUC 0.63 and 0.69 respectively). These results are consistent with the previous composite biomarker findings that integrative indices are better than single-marker methods [21]. Directly in Figure 3, the ROC curves are indication of the better discrimination of the CDI.

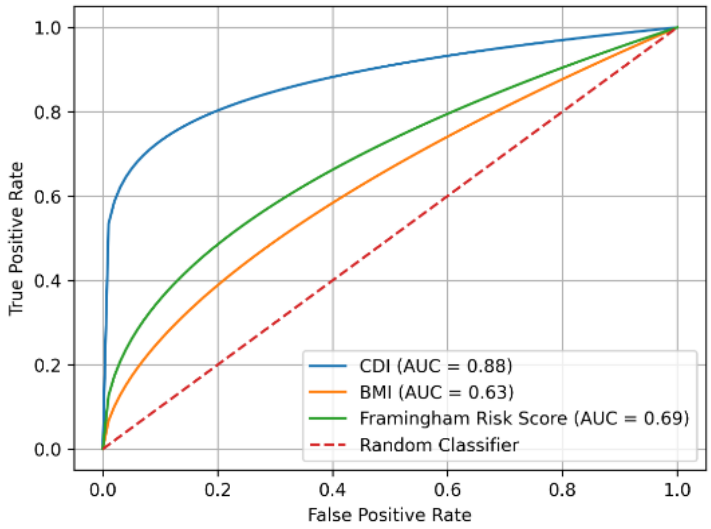

Figure 3. ROC Curves for Prediction of 24-Month Metabolic Syndrome Incidence by the Combined Dysbiosis Index and Individual Microbiome Parameters. AUC Values and 95% CIs are Displayed for Each Predictor

4.4. Longitudinal Microbiome and Metabolic Trajectories

Follow-up analysis (24 months) of longitudinal data showed that there were progressive differences in the microbial composition and metabolic parameters between the groups. Table 4 illustrates that the Shannon diversity index in Met-S progressors was decreasing at a significant trend as indicated by the p value of 0.001 since baseline (3.41) to 2.97 (at 24 months) whereas non progressors did not vary significantly over time. F/B ratio of progressors rose steadily in progression between 3.82 and 5.12 ($p<0.001$) indicating a gradual shift to F/B Firmicutes predominance, with deteriorating metabolic parameters. Figure 4 shows that the longitudinal trends of these indices of microbiome between groups are divergent.

Table 4. Longitudinal Trajectories of Gut Microbiome and Metabolic Parameters in Met-S Progressors vs. Non-Progressors

Parameter	Baseline	12 Months	24 Months	p (Trend)
Shannon Index – Met-S	3.41±0.52	3.18±0.48	2.97±0.51	<0.001
Shannon Index – No Met-S	4.18±0.48	4.21±0.46	4.19±0.49	0.84
F/B Ratio – Met-S	3.82±1.14	4.41±1.28	5.12±1.43	<0.001
F/B Ratio – No Met-S	2.21±0.87	2.18±0.84	2.24±0.91	0.79
HOMA-IR – Met-S	2.9±1.1	3.6±1.3	4.2±1.4	<0.001
HOMA-IR – No Met-S	1.8±0.7	1.9±0.7	1.8±0.8	0.71
CRP (mg/L) – Met-S	3.2±1.8	4.6±2.1	5.9±2.4	<0.001
Butyrate (µmol/g) – Met-S	12.4±3.8	9.8±3.2	7.6±2.9	<0.001
Butyrate (µmol/g) – No Met-S	22.1±4.6	22.8±4.4	23.1±4.9	0.68

Fecal butyrate levels decreased gradually in Met-S progressors (12.4 to 7.6 1/g, $p<0.001$) went hand in hand with rising HOMA-IR (2.9 to 4.2) and hs-CRP (3.2 to 5.9 mg/L), providing support to a mechanistic model where the reduction of SCFA production spurred progressive Spearman correlation analysis was used to affirm an inverse relationship between baseline Shannon diversity and 24 months HOMA-IR ($r= -0.58$, $p<0.001$), fasting glucose ($r= -0.49$, $p<0.001$), and hs-CRP ($r= -0.52$, $p<0.001$), and positive relationships between F/B ratio The level of lipopolysaccharide-binding protein (LBP) was significantly elevated at all time points in Met-S progressors and to a progressive extent, which corroborates the theory that the intestinal permeability triggered by dysbiosis and bacterial translocation is a factor in the inflammatory environment leading to metabolic syndrome [22].

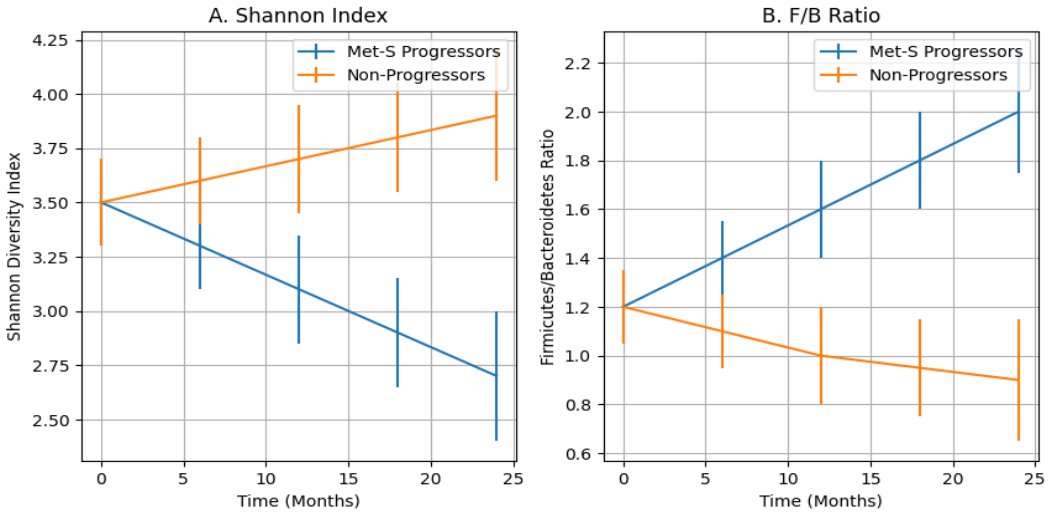

Figure 4. Longitudinal Trajectories of Alpha Diversity (Shannon Index) and Firmicutes/Bacteroidetes Ratio from Baseline to 24 Months. Red: Met-S Progressors; Blue: Non-Progressors. Error Bars Represent ±SD

4.5. Discussion of Mechanistic Implications

The results of the present paper confirm the existence of a mechanistic paradigm where the dysbiosis of the gut microbiome comes before and plays a role in the development of metabolic syndrome via interrelated mechanisms. To begin with, low populations of those bacteria generating butyrate mean lesser luminal availability of butyrate, disrupting the energy metabolism of colonocytes and the fixation of tight junctions. Impaired epithelial integrity contributes to translocation of microbial products, such as LPS, into portal circulation, SDTLR4 (TLR4) signaling in adipose tissue, liver, and skeletal muscle, which leads to low-grade systemic inflammation and impaired insulin signaling [23].

Second, the loss of A. muciniphila that happens in Met-S progressors has a mechanical meaning. It is a key controller of mucus layer viscosity, gut barrier integrity and its presence has been negatively associated with the presence of endotoxins in the bloodstream and insulin resistance. Randomized trials have shown that A. muciniphila supplementation may raise the insulin sensitivity and lipid profiles of metabolically disabled individuals, which is another way that supports this bacterium as an important metabolic-protective commensal [14]. Third, the increased F/B ratio of progressors indicates a transition to more energy-harvesting microbial communities with the Firmicutes having a higher potential to extract calories in dietary polysaccharide potentially contributing to adiposity generation not dependent on dietary intake [9].

The progressive dysbiosis process seen in Met-S progressors indicates that there may be a self-perpetuating dysbiosis process, in which metabolic function is impaired by initial dysbiosis, which in turn further selects against favorable taxa, which further changes metabolic functionality which in turn favors those taxa even more. The implications of this cycle are significant to the timing of interventions as the microbiome-targeted intervention can possibly do best when applied at the dysbiotic phase before the required Met-S criteria is completely achieved [24]. The CDI provides a clinically practical method to microbiome risk information operationalization, making interpretation easier but getting the multidimensionality of dysbiosis. Significantly, dietary manipulations fundamentally alter the microbiome, and high-fiber diets were shown to be an effective method to significantly increase the number of beneficial taxa in weeks, which is why the concept of identifying microbiome risks at an early stage is useful to serve as a foundation of actionable nutritional prescriptions [25].

4.6. Study Strengths and Limitations

The main strengths of the research are that it has a prospective design, targets a younger adult population that has been underexplored in previous microbiome-metabolic cohort studies, is longitudinally followed with high retention (94.3%), and the creation and internal validation of the CDI

composite index. Limitations consist in the single-center recruitment (which reduces generalizability); relying on 16S rRNA amplicon sequencing (which does not offer much functional resolution with respect to whole-genome shotgun metagenomics); the dietary assessment based on validated food frequency questionnaires but not on objective dietary biomarkers; the observational nature of the study that prevents conclusive causation.

5. CONCLUSION

This is a prospective observational cohort study that shows that gut microbiome dysbiosis at baseline is a strong and independent predictor of the development of metabolic syndrome in overweight young adults during a 24-month follow-up time. The metabolic syndrome dysbiotic signature in Met-S progressors included reduced alpha diversity, increased Firmicutes/Bacteroidetes ratio, loss of Akkermansia muciniphila and Faecalibacterium prausnitzvi, decreased butyrate-producing taxa and lower fecal butyrate levels, all observed prior to the development of any clinical metabolic syndrome criterion. These microbiome changes were gradually enhanced through time in parallel with the increasing impairment of metabolic and inflammatory parameters that render the hypothesis of a mechanistic and even causal position of dysbiosis in the metabolic worsening.

Combined Dysbiosis Index, which combined several microbiome parameters in one composite score, had a better predictive accuracy (AUC 0.88) than either given microbiome measure or traditional clinical risk factors validating its ability to be a clinically translatable predictor of risk stratification. Microbiome-based identification of at-risk individuals may allow targeted prevention methods, such as dietary fiber supplementation, focused probiotic actions, and high-intensity lifestyle change, to be implemented at the key point when the metabolic syndrome is forming, which could lead to decreased cardiometabolic disease burden in young adults over the long-term.

The future areas of research need to address the international validation of CDI on a multi-center scale, parallel whole-genome metagenomics analyses to address functional microbiome pathways, and randomized controlled trials assessing the ability of microbiome-targeted interventions in CDI-high individuals to reduce incident Met-S. Profiling of microbiomes of the gut has become a promising frontier of precision medicine and can provide mechanistically based, modifiable, and early predictive, potentially unavailable to current biomarker panel approaches.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Omar Qahtan Yaseen	✓	✓	✓	✓		✓		✓	✓	✓	✓			

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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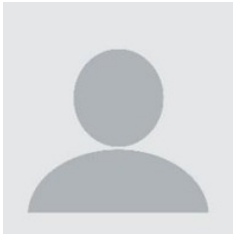

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