

Article

Associations Between the Maternal Blood Microbiome During Pregnancy and Early Childhood Growth Trajectories: A Pilot Study

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Abstract

Objective: Maternal blood microbiome signatures during pregnancy have been linked to adverse birth outcomes. We conducted a pilot study to examine whether they are also associated with early childhood growth in offspring and to explore maternal metabolites as potential mediators of these relationships. **Methods:** This study included 50 mother-child dyads from a prospective pregnancy cohort. Children were selected based on distinct body mass index (BMI) growth trajectories from birth to 4 years, including 25 children in a rising-high-BMI trajectory and 25 in a low-BMI trajectory. Maternal plasma collected during the second trimester underwent 16S rRNA gene sequencing for microbial profiling and an untargeted metabolomics analysis. Microbial diversity indices were compared between groups. Multivariable logistic regression models assessed associations between microbial taxa and BMI trajectories with adjustment for covariates. Mediation analyses evaluated whether maternal metabolites mediated observed associations. **Results:** Higher maternal blood microbial α -diversity was observed among mothers of children in the rising-high-BMI trajectory. Greater abundance of *Gammaproteobacteria*/*Proteobacteria* (class/phylum) was associated with lower odds of membership in the rising-high-BMI trajectory, whereas *Bacteroidia*/*Bacteroidota* and *Actinobacteria*/*Actinobacteriota* were associated with a greater risk. Mediation analyses identified several maternal metabolites that potentially linked prenatal microbial taxa to child growth outcomes. Key mediators included metabolites involved in benzoate metabolism (e.g., 4-vinylphenol sulfate for taxa *Gammaproteobacteria*/*Proteobacteria*), lipid metabolism (e.g., 1-linoleoyl-GPG (18:2) for *Bacteroidia*/*Bacteroidota*), glutathione metabolism (cysteinylglycine disulfide for *Bacteroidia*/*Bacteroidota*), branched-chain amino acid metabolism (3-hydroxy-2-ethylpropionate for *Bacteroidia*/*Bacteroidota*), histidine metabolism (imidazole propionate for *Actinobacteria*/*Actinobacteriota*), and TCA cycle (glutaconate for *Actinobacteria*/*Actinobacteriota*). These pathways are implicated in oxidative stress, adipocyte differentiation, insulin signaling, and energy metabolism, processes that are highly relevant to obesity development. **Conclusion:** Findings suggest that prenatal blood microbial signatures may influence early childhood growth through metabolic pathways related to obesity. These pilot study findings support further investigation into the role of prenatal blood microbial signatures in child development and health outcome prediction in larger studies.



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1. Introduction

The prevalence of childhood obesity continues to rise in the United States, nearly doubling over the past three decades, with no indication that this trend is slowing. According to the most recent data from the CDC, the prevalence of obesity among U.S. children and adolescents is 19.7%, affecting approximately 14.7 million youths aged 2–19 years [1]. In line with the Developmental Origins of Health and Disease (DOHaD) framework, a growing body of evidence suggests that maternal conditions during pregnancy, which can translate into fetal intrauterine exposures, are associated with obesity risk in offspring [2–4]. However, scientific understanding of the prenatal programming of offspring obesity is quite limited. There is an urgent need to identify etiologic processes and predictors in order to develop effective strategies to reduce the risk of developing childhood obesity.

Recent studies support the important role of the microbiota at various body sites in pregnancy complications and adverse fetal outcomes, such as gestational diabetes mellitus (GDM) [5,6], preeclampsia [7–9], fetal growth restriction [10–12], and preterm birth [13–15]. For example, changes in the gut microbiota during pregnancy have been reported to predict the onset of GDM, even weeks before its typical clinical diagnosis [16]. A recent systematic review and meta-analysis also found significantly lower gut microbiota α -diversity, measured by the Shannon index, in pregnant women with preeclampsia compared with healthy controls [8]. Although the gut microbiota during pregnancy has been studied most extensively, alterations in maternal microbiota at other body sites, including the placenta and vagina, have also been associated with fetal growth restriction and preterm birth [10–15]. These pregnancy and fetal health conditions reflect an adverse intrauterine environment that can significantly influence child health outcomes after birth, including growth trajectories and obesity risk [4,17–21].

The blood microbiome has recently emerged as a novel area of research for understanding disease pathogenesis and improving risk prediction. Once thought to be sterile, human blood is now known, through advances in next-generation sequencing, to contain microbial genetic material even in healthy individuals. Although debate remains about whether these signals represent viable microbes or microbial cell-free DNA (cfDNA), evidence suggests they may originate from multiple body sites, including the gut, skin, and oral cavity [22]. Increasing evidence has linked blood microbial signatures to a range of diseases, including cardiometabolic and inflammatory disorders [23]. However, the role of the prenatal blood microbiome in shaping fetal and child health remains largely unexplored. A few studies have detected complex microbial cfDNA profiles in the blood of healthy pregnant women and suggested potential links to pregnancy outcomes such as preterm birth and stillbirth, though these studies were limited by small sample sizes [24,25]. Significant knowledge gaps remain regarding the dynamics of the maternal blood microbiome during pregnancy and their potential influence on birth outcomes and postnatal growth. Understanding these relationships may reveal novel mechanisms underlying the early-life programming of health and disease.

One potential mechanism linking the maternal microbiome and fetal development is the production of bioactive metabolites by microbiota. These metabolites can enter the maternal circulation and may be actively or passively transferred across the placenta [26]. In animal models, trimethylamine N-oxide, a metabolite regulated by maternal gut microbes, has been shown to promote thalamic axon outgrowth in offspring [27]. In addition, short-chain fatty acids (SCFAs), another major class of microbiota-derived metabolites, are

transported from the maternal gut to the fetus via the placenta. Maternal conditions such as GDM and obesity can alter SCFA production, potentially impairing fetal cardiovascular, neural, and immune development and predisposing offspring to adverse health outcomes later in life [28]. However, no studies to date have systematically identified metabolites that mediate the effects of the circulating microbiome on fetal development and childhood health outcomes.

Therefore, we conducted this pilot study to examine the relationship between prenatal blood microbiome and early childhood body mass index (BMI) growth trajectories using data from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort, which demonstrates a broad range of obesity risk, ideal for testing these models. BMI trajectories leveraged repeated anthropometric measurements and may offer improved prediction of later-life obesity risk compared to a single growth measurement [29]. In addition, we explored the metabolites that might mediate the relationship between prenatal blood microbiome and child growth outcomes using untargeted metabolomics data collected from CANDLE mothers during pregnancy.

2. Methods

2.1. Study Participants

All the study participants were from the CANDLE study, a prospective pregnancy cohort of mother-child dyads in Shelby County, Tennessee (Memphis and surrounding areas). Accrued between 2006 and 2011, a total of 1503 participants aged 16–40 years during their second trimester of pregnancy with 1455 live births were enrolled in the CANDLE study [30,31]. The inclusion and exclusion of CANDLE participants have been reported previously [31]. In general, the CANDLE sample demographically represents Shelby County, and nearly two-thirds of the participants are Black ($N = 953$; 65.5%). In a previous study, we observed three BMI trajectory groups among the CANDLE children, the rising-high- (12.2%), moderate- (66.5%), and low-BMI (21.3%) trajectories [4]. The children in the rising-high-BMI trajectory were characterized as having an average birthweight followed by a rapid weight gain during the first year and staying at a stable high BMI level until 4 years old. The low-BMI trajectory had a relatively lower birthweight and rapid growth during the first year but still stayed at a relatively lower BMI. The moderate-BMI trajectory group was in the middle of the rising-high- and the low-BMI trajectory groups, representing the majority of the children. For the present study, to minimize confounding, we restricted our focus to Black families (the predominant self-identified group in the cohort) and we randomly selected 25 children from the rising-high-BMI trajectory group and 25 from the low-BMI trajectory group as cases and controls, respectively, to compare their mothers' blood microbiome during the second trimester of pregnancy.

2.2. Maternal Data Collection

The mother's sociodemographic information (age, race, education, insurance type, and marital status), health behaviors (cigarette smoking and alcohol use during pregnancy), parity, and medical history were collected by self-administered questionnaires at enrollment during the second trimester. Self-reported height and weight before pregnancy were collected at enrollment and used to calculate pre-pregnancy BMI as weight (in kilograms) divided by the square of height (in meters). Pregnancy complications and medical updates were obtained since the third trimester visit through an interview of the mother by the study staff and confirmed by medical chart abstraction [32].

2.3. Child Measures

Birth weight and length of the children were extracted from medical charts by research assistants. Body weight and length/height were also measured at each annual visit until 4 years of age using the methods guided by the NHANES protocol [33]. The sex- and age-specific BMI-z-scores for each child were calculated based on the World Health Organization growth standards (<2 years) and the Center for Disease Control and Prevention (CDC) growth charts (≥ 2 years) following CDC recommendations [34]. The BMI-z-scores were used to analyze the growth trajectories among the CANDLE children using the latent class growth modeling approach [4].

2.4. Prenatal Blood Microbiome Analysis

The prenatal blood microbiome profiling was conducted by the Center for Metagenomics and Microbiome Research at Baylor College of Medicine (CMMR). Briefly, DNA was extracted from 200 μ L plasma samples collected during the second trimester from the mothers using the Qiagen DNeasy Blood and Tissue Kit (QIAGEN Inc., Germantown, MD, USA). The 16Sv4 rDNA region was amplified by PCR using the universal primers 515F and 806R and sequenced on the Illumina MiSeq platform (Illumina, Inc., San Diego, CA, USA) using the 2 $\times$ 250 bp paired-end protocol. A stringent contamination control protocol was implemented. To isolate potential contamination at specific workflow steps, multiple controls are included during DNA extraction and library preparation, including extraction blanks, PCR blanks, and commercial mock communities.

Raw data files in binary base call format were converted into FASTQs and demultiplexed based on the single-index barcodes using the Illumina 'bcl2fastq' software. Demultiplexed read pairs underwent initial quality filtering using bbdut.sh (BBMap version 38.82.5), removing Illumina adapters, PhiX reads and reads with a Phred quality score below 15 and length below 100 bp after trimming. Quality-controlled reads were then merged using bbmerge.sh (BBMap version 38.82.5), with merge parameters optimized for the 16SV4 amplicon type (maxstrict = t, qtrim = t, trimq = 15). Merged reads were then further filtered using VSEARCH, allowing for a maximum expected error of 0.05, a maximum length of 254 bp and a minimum length of 252 bp [35]. All the reads were combined into a single FASTA file for further processing.

Resulting reads were clustered into OTUs at a similarity cutoff of 97% via the UPARSE algorithm [36] using an in-house iterative stepwise approach that includes chimera filtering [37]. Briefly, reads were first dereplicated using the VSEARCH "derep_fulllength" option and recording the size to identify singletons. The dereplicated non-singleton reads were clustered through an iterative stepwise manner in increments of 0.4% using usearch70 "cluster_otus" function. Singletons were mapped back to the dereplicated reads using usearch70 "-usearch_global" at a 99% identity, and mapped reads were added to the output. The final output was run through usearch70 'uchime_ref' program against the GOLD database [38], using only the plus strand and allowing for no chimeras, in order to create a clustered OTU file with no chimeras. The data were then rarefied for analyses. The OTU centroids file was mapped against an optimized version of the latest current SILVA Database [39] containing only sequences from the v4 region of the 16S rRNA gene to determine taxonomies using the usearch70 "usearch_global" function [40], specifying the identity threshold to 97%. The V4 region of the 16S rRNA gene might provide good resolution at the genus level [41]. The detected genera were further filtered against the list of potential contaminating genera for quality control [42].

2.5. Prenatal Metabolomics Analysis

Maternal plasma samples collected in the second trimester were used to conduct prenatal metabolomic profiling. An untargeted metabolomics analysis was performed using the Metabolon Discovery HD4TM Platform (Metabolon Inc., Morrisville, NC, USA), which includes four ultra-high-performance liquid chromatography-mass spectrometry methods. More details of the metabolomics analysis have been previously reported [43]. A total of 949 metabolites with known structural identity (named biochemicals) were identified in the study samples. After excluding 69 metabolites with missing/below-the-detection-limit > 80% of the samples, 880 metabolites were included in the present study.

2.6. Data Analysis

Clinical characteristics of the rising-high-BMI and low-BMI trajectory groups were compared using *t*-tests for continuous variables and chi-square tests for categorical variables. Fisher's exact tests were used instead of chi-square tests when cell counts were small, including for education (>high school), cigarette smoking and alcohol use during pregnancy. Microbial α -diversity indices, including Observed OTUs, Shannon, Chao1, Simpson, and InvSimpson, were calculated and compared between the two BMI trajectory groups using the Wilcoxon rank-sum test. β -diversity was assessed using Bray–Curtis, Jaccard, and robust Aitchison dissimilarities. Principal coordinates analysis (PCoA) implemented in the R package *vegan* was used to visualize group differences, and the permutational multivariate analysis of variance method (PERMANOVA) was used to test differences across groups for each distance metric. To identify and prioritize microbiota associated with the outcome, we examined the associations between the rarefied abundance of each bacterial taxon and the risk of membership into the rising-high-BMI trajectory group using multivariable logistic regression models. The models were adjusted for potential confounders, including maternal age at pregnancy, prepregnancy BMI, socioeconomic status (education and insurance type), lifestyle factors (smoking and alcohol consumption), parity, and antibiotic use.

To explore whether the associations between prenatal blood microbiota and BMI growth trajectories in offspring were mediated by prenatal metabolite outcomes, we first identified the metabolites that were associated with the identified outcome-associated microbiota (exposure variables) and also associated with BMI trajectories (outcome variables) at a significance level of *p* value < 0.10. We then evaluated whether these metabolites mediated the associations between prenatal microbiota and study outcomes using the R package *mediation* [44]. The same set of covariates as used in the logistic regression analysis was included in the mediation models.

3. Results

3.1. Characteristics of the Study Subjects

The characteristics of the study mothers and children in the rising-high-BMI and low-BMI trajectory groups are shown in Table 1. The average age (SD) of the mothers at pregnancy, education levels, health insurance, smoking and alcohol drinking status, and parity did not differ significantly between the trajectory groups (all *p* > 0.05). However, mothers of children in the rising-high-BMI group had a higher prepregnancy BMI level than those whose children were in the low-BMI group (*p* = 0.03). The gestational age at birth did not differ significantly between the two groups (*p* = 0.09). Children in the rising-high-BMI group had higher birthweight and BMI-z-scores at ages 1, 2, 3, and 4 years (all *p* < 0.05).

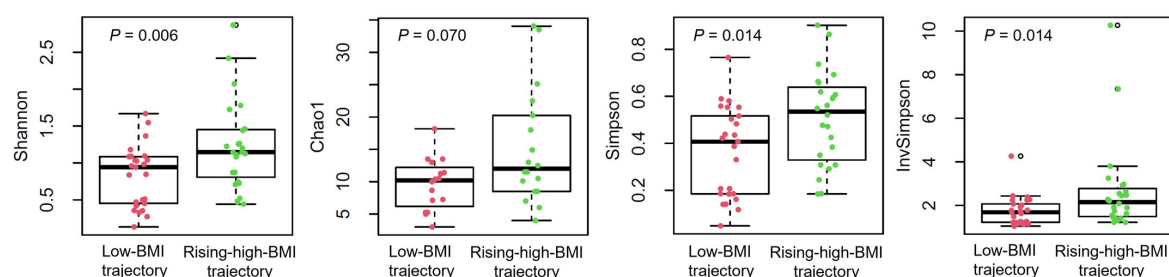
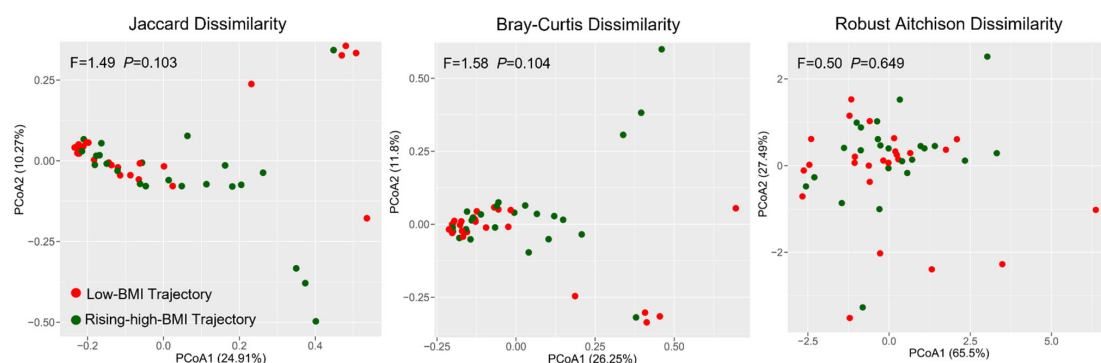
Table 1. Characteristics of study participants.

Variables	Low-BMI Trajectory (N = 25)	Rising-High-BMI Trajectory (N = 25)	p Value
Maternal			
Age, years	24.4 (4.7)	26.6 (6.7)	0.188
More than high school, %	20.0	16.0	1.000
Medicaid, %	80.0	80.0	1.000
Smoking, %	8.0	20.0	0.417
Alcohol drinking, %	12.0	16.0	1.000
Parity (primiparous), %	36.0	28.0	0.762
Pre-pregnancy BMI, kg/m ²	26.9 (7.2)	32.6 (10.4)	0.030
Child			
Male, %	48.0	48.0	1.000
Gestational age at birth, week	38.9 (1.0)	39.4 (1.1)	0.090
Birth weight, kg	3.0 (0.3)	3.3 (0.5)	0.007
Birth length, cm	50.4 (2.1)	50.0 (2.9)	0.650
BMI-z-score at birth	−1.39 (0.86)	−0.16 (1.10)	<0.001
BMI-z-score at age 1	−0.20 (1.18)	2.83 (1.26)	<0.001
BMI-z-score at age 2	−1.05 (1.28)	2.17 (0.89)	<0.001
BMI-z-score at age 3	−0.80 (0.73)	2.30 (1.05)	<0.001
BMI-z-score at age 4	−0.72 (0.85)	1.99 (0.97)	<0.001

BMI, body mass index. Continuous variables are means (standard deviations).

3.2. Diversity Analyses

Almost all α -diversity indices we examined were significantly higher in mothers of children in the rising-high-BMI trajectory group compared with those in the low-BMI group ($p < 0.05$), except for the Chao1 index ($p = 0.07$) (Figure 1). Differences in β -diversity between the two trajectory groups were visualized using PCoA plots (Figure 2). Although none of the three β -diversity metrics reached statistical significance, a trend toward separation between the two growth trajectory groups was observed in the PCoA plots based on the Jaccard and Bray–Curtis dissimilarity indices ($p = 0.102$ and 0.104 , respectively).

**Figure 1.** Comparisons of α -diversity indices between the low-BMI and rising-high-BMI trajectory groups.**Figure 2.** PCoA plots of β -diversity indices.

3.3. Taxonomic Composition of Prenatal Blood Microbiota

Taxonomic profiling of the prenatal blood microbiota identified a total of 48 genera, 35 families, 27 orders, 12 classes, and 7 phyla. Figure 3 shows the top 10 genera based on relative abundance.

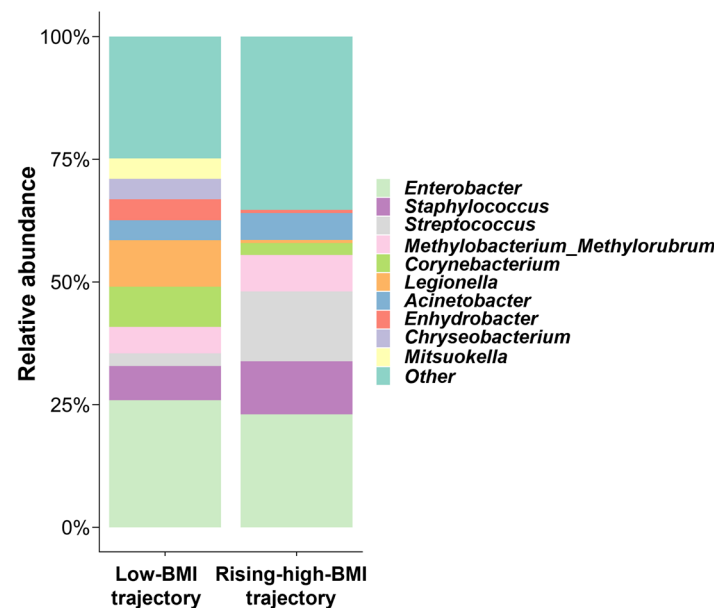


Figure 3. Taxonomic composition bar plot in the different trajectory groups at the genus level.

3.4. Associations Between Prenatal Blood Microbiota and Child Growth Trajectories

After adjusting for potential confounders, several bacterial taxa were associated with BMI trajectories at a significance level of $p < 0.10$ (most of p values < 0.05) (Table 2). Higher abundance of class *Gammaproteobacteria* and its parent phylum *Proteobacteria* was associated with a lower risk of membership in the rising high-BMI trajectory group (both $p < 0.05$). In contrast, class *Bacteroidia* and its phylum *Bacteroidota* were associated with an increased risk of membership in the rising high-BMI trajectory group (both $p < 0.05$). Class *Actinobacteria* and its phylum *Actinobacteriota* showed suggestive positive associations with the risk of membership in the rising high-BMI trajectory group ($p = 0.050$ and 0.093 , respectively).

Table 2. Prenatal blood microbiota at different taxonomic levels associated with the rising-high-BMI trajectory group in children at a p value < 0.10 .

Taxa	OR (95% CI)	<i>p</i> Value
Class		
<i>Gammaproteobacteria</i>	0.91 (0.84, 0.99)	0.030
<i>Bacteroidia</i>	1.82 (1.05, 3.15)	0.032
<i>Actinobacteria</i>	1.32 (1.00, 1.75)	0.050
Phylum		
<i>Proteobacteria</i>	0.90 (0.83, 0.99)	0.026
<i>Bacteroidota</i>	1.82 (1.05, 3.15)	0.032
<i>Actinobacteriota</i>	1.24 (0.94, 1.59)	0.093

3.5. Metabolite Mediators Linking Prenatal Blood Microbiota and Child Growth Outcomes

Mediation analyses identified several maternal metabolites that potentially linked prenatal blood microbial taxa to childhood growth trajectories with p values of mediation effects < 0.10 (Table 3). At both class and phylum levels, associations for *Gammaproteobacteria* / *Proteobacteria* were mediated by benzoate-related metabolites (e.g., 4-vinylphenol sulfate

and 4-hydroxyhippurate), phytanate, and lysophospholipids, with mediation proportions ranging from approximately 20% to 38%. For Bacteroidia/Bacteroidota, glutathione-related (cysteinylglycine disulfide), benzoate-related, and lysophospholipid metabolites showed positive mediation effects (22%–41%), whereas 3-hydroxy-2-ethylpropionate demonstrated inverse mediation ($\sim -22\%$). Actinobacteria/Actinobacteriota exhibited the strongest signals, particularly through glutaconate (TCA cycle; $\sim 42\%$), along with 3-hydroxypyridine sulfate and imidazole propionate.

Table 3. Prenatal Metabolites Mediating the Efforts of Prenatal Blood Microbiota on BMI Growth Trajectories in Children.

Taxa	Metabolite Mediator	Metabolic Pathway	<i>p</i> Value of Mediation Effect	Proportion Mediated, %
Class				
<i>Gammaproteobacteria</i>	4-vinylphenol sulfate	Benzoate Metabolism	0.052	27.3
	3beta-hydroxy-5-cholestenoate	Sterol	0.064	22.1
	phytanate	Food Component/Plant	0.070	26.6
	1-linoleoyl-GPG (18:2)	Lysophospholipid	0.082	32.1
<i>Bacteroidia</i>	cysteinylglycine disulfide	Glutathione Metabolism	0.064	37.5
	3-hydroxy-2-ethylpropionate	Leucine, Isoleucine and Valine Metabolism	0.084	−21.5
	4-hydroxyhippurate	Benzoate Metabolism	0.084	39.4
	1-linoleoyl-GPG (18:2)	Lysophospholipid	0.096	22.6
<i>Actinobacteria</i>	glutaconate	TCA Cycle	0.030	42.1
	3-hydroxypyridine sulfate	Chemical	0.054	33.9
	imidazole propionate	Histidine Metabolism	0.098	18.5
Phylum				
<i>Proteobacteria</i>	phytanate	Food Component/Plant	0.074	27.7
	2-piperidinone	Food Component/Plant	0.078	20.8
	4-vinylphenol sulfate	Benzoate Metabolism	0.084	28.2
	4-hydroxyhippurate	Benzoate Metabolism	0.090	37.8
<i>Bacteroidota</i>	cysteinylglycine disulfide	Glutathione Metabolism	0.056	38.9
	4-hydroxyhippurate	Benzoate Metabolism	0.066	40.9
	1-linoleoyl-GPG (18:2)	Lysophospholipid	0.080	21.9
	3-hydroxy-2-ethylpropionate	Leucine, Isoleucine and Valine Metabolism	0.086	−22.1
<i>Actinobacteriota</i>	glutaconate	TCA Cycle	0.032	41.9
	3-hydroxypyridine sulfate	Chemical	0.066	31.4
	1-linoleoyl-GPG (18:2)	Lysophospholipid	0.072	26.2
	imidazole propionate	Histidine Metabolism	0.096	19.5

4. Discussion

In this pilot study, we detected and characterized maternal prenatal blood microbiome signatures that were associated with early childhood growth trajectories. We also identified potential prenatal metabolite mediators linking the prenatal blood microbiome signatures with the child growth outcome. These findings support further investigations of prenatal blood microbiome for predicting and understanding the early origins of child health outcomes.

We observed that higher prenatal maternal blood microbiome α -diversity was associated with offspring who had normal birth weight but exhibited rapid postnatal weight gain (rising-high-BMI trajectory), compared to those with relatively lower birth weight and

slower subsequent growth (low-BMI trajectory). Greater microbial α -diversity within a low-biomass compartment such as maternal blood should not be interpreted as inherently beneficial. In contrast to the gut, where higher diversity often reflects ecological stability, greater diversity detected in circulation may signal enhanced microbial translocation, barrier perturbation, or low-grade systemic inflammation rather than a structured resident community [45]. Notably, greater blood microbial diversity has been observed in pregnant women who delivered preterm compared with those who delivered at full term [25]. Circulating bacterial DNA fragments and pathogen-associated molecular patterns can arise from increased intestinal permeability and have been implicated in metabolic endotoxemia, inflammatory activation, and obesity development [46–48]. During pregnancy, even subtle elevations in systemic inflammatory level may influence placental signaling, nutrient transport, and fetal tissue differentiation [49]. Experimental and epidemiologic evidence suggests that maternal immune and metabolic status shapes fetal adipogenesis, insulin sensitivity, and hypothalamic appetite regulation, thereby programming postnatal growth trajectories [50]. In this context, higher circulating microbial diversity may reflect heterogeneous microbial exposure that amplifies inflammatory or metabolic signaling during gestation, priming offspring for enhanced energy storage efficiency and accelerated postnatal weight gain despite normal birth weight. Conversely, lower diversity in maternal blood may indicate reduced microbial translocation or systemic inflammatory levels, potentially corresponding to relatively normal in utero growth.

In this study, several prenatal blood microbial taxa were associated with BMI growth trajectories in early childhood. At the phylum level, taxa *Proteobacteria*, *Bacteroidota*, and *Actinobacteriota* have been reported as dominant groups within the human circulating microbiome [25]. Higher abundances of *Gammaproteobacteria* and its parent phylum *Proteobacteria* in maternal blood during pregnancy were associated with lower odds of children being classified into the rising high-BMI trajectory group. In contrast, enrichment of *Bacteroidia* (phylum *Bacteroidota*) and *Actinobacteria* (phylum *Actinobacteriota*) were positively associated with increased risk of membership in the rising high-BMI trajectory group. Alterations in the abundance of *Bacteroidota* and *Actinobacteriota* have previously been linked to obesity and metabolic dysfunction, although findings are heterogeneous [51–54]. Members of *Bacteroidia* in gut are major producers of immunologically active lipopolysaccharides that can influence host inflammatory tone and insulin signaling, pathways central to adiposity development [55]. Increased exposure to such microbial components during pregnancy, potentially via translocation into maternal circulation, may alter placental immune signaling and nutrient transport, thereby influencing fetal adipocyte differentiation and energy homeostasis. *Actinobacteria* have been associated with obesity in children and with type 2 diabetes and metabolic syndrome in adults [53,56].

Conversely, the inverse association observed for *Proteobacteria* is noteworthy given that expansion of *Proteobacteria* in the gut is often considered a marker of dysbiosis and inflammation [57]. However, associations between *Proteobacteria* and obesity are inconsistent in previous studies, and shifts in relative abundance may reflect broader microbial community changes rather than direct causal effects [58]. In the context of maternal blood, a low-biomass environment, these taxa likely represent differential microbial translocation rather than a stable circulating microbial community. One possible interpretation is that relative enrichment of *Bacteroidota* and *Actinobacteriota*, together with lower levels of *Proteobacteria*, may indicate a maternal immune-metabolic environment that favors obesogenic fetal programming. Future studies with species-level resolution, functional microbial profiling, and detailed maternal inflammatory and metabolic markers will be important to determine whether these taxa contribute mechanistically to offspring adiposity or simply act as biomarkers of maternal physiological states during pregnancy.

Mediation analyses identified maternal metabolites that potentially mediate the associations between prenatal blood microbial taxa and childhood growth trajectories in offspring. Three phyla, *Proteobacteria*, *Bacteroidota*, and *Actinobacteriota*, may influence childhood obesity risk through distinct yet converging metabolic pathways rooted in microbial-host co-metabolism. For *Proteobacteria*, metabolites such as phytanate and aromatic sulfated compounds including 4-hydroxyhippurate may affect fetal adiposity development by modulating peroxisomal β -oxidation, PPAR signaling, and inflammatory tone in utero, processes that can program lipid storage and energy balance in the offspring [59,60]. In *Bacteroidota*, mediators such as cysteinylglycine disulfide (reflecting glutathione turnover and oxidative stress), 1-linoleoyl-GPG (18:2) (a lysophospholipid indicating membrane lipid remodeling), and 3-hydroxy-2-ethylpropionate (linked to branched-chain amino acid and intermediary carbon metabolism) could influence fetal growth and adipocyte differentiation by shaping oxidative stress status, membrane composition, and nutrient sensing, which may alter metabolic set points in early life [61]. *Actinobacteriota*-associated metabolites, including glutaconate (intermediary carbon metabolism) and imidazole propionate (histidine-derived microbial metabolite), may program insulin signaling and mitochondrial energy utilization in the developing fetus. Specifically, imidazole propionate, a microbial-derived metabolite, can impair insulin receptor signaling via the p38 γ /p62/mTORC1 pathway, potentially promoting early insulin resistance and predisposing the child to postnatal obesity [62].

The primary limitations of this study include the modest sample size and the use of a less stringent significance threshold without adjustment for multiple testing. Therefore, the results should be interpreted with appropriate caution. Nevertheless, as a pilot investigation, this study provides important preliminary evidence suggesting a potential role of the prenatal blood microbiome in shaping child development. By integrating prenatal metabolomic biomarkers, we identified microbially derived metabolites as potential mediators, further supporting a mechanistic link between the prenatal blood microbiome and child developmental outcomes. Future studies are still needed to examine the causal relationship between the outcome-related prenatal blood microbiota and metabolite mediators. Another limitation is that the RNA-sequencing approach could not distinguish the origin of the detected microbial signatures, whether from viable microbiota or from bacterial genetic material translocated into the circulation from other body niches. However, many of the major microbial members identified in this study have been reported in previous blood microbiome studies, supporting the biological plausibility of our findings [22,63].

In conclusion, our findings provide novel preliminary evidence supporting a potential role of the prenatal blood microbiome in early childhood growth. Maternal metabolites may act as mechanistic mediators linking the prenatal blood microbiome to intrauterine adiposity programming, thereby influencing postnatal growth trajectories. Larger, well-powered studies with more comprehensive profiling of blood microbial communities, including species- and strain-level resolution, are needed to further elucidate these associations and confirm their relevance for obesity etiology and prevention.

Author Contributions: Conceptualization, Q.Z.; Methodology, Q.Z.; Formal analysis, Q.Z., C.-Y.C. and L.H.; Resources, Q.Z., J.L., N.R.B. and K.Z.L.; Writing—original draft, Q.Z., C.-Y.C., L.H., A.J.G.R. and J.L.; Writing—review & editing, Q.Z., C.-Y.C., L.H., A.J.G.R., J.L., K.Z.L. and N.R.B.; Supervision, Q.Z.; Funding acquisition, Q.Z. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The CANDLE study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Review Board of the University of Tennessee Health Science Center (Study ID: 06-08495-FB).

Informed Consent Statement: Informed consent was given by participants 18 years or older, while assent was given by those less than 18 years and consent was provided by their legally authorized representative prior to enrollment.

Data Availability Statement: The data are not publicly available due to privacy or ethical restrictions. However, the data presented in this study are available on request from the corresponding author.

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