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Maternal gut microbiota in the postpartum Period: A Systematic review

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Abstract

Studies have demonstrated the importance of the gut microbiota during pregnancy, and there is emerging literature on the postpartum maternal gut microbiota. The primary objective of this paper was to synthesize the literature on the postpartum gut microbiome composition and diversity measured in stool samples from healthy mothers of predominantly term infants. The secondary objectives were (1) to identify biological and environmental factors that influence postpartum maternal gut microbiota and (2) to assess health conditions and clinical intermediate measures associated with postpartum gut microbiota changes in all mothers. Electronic searches were conducted November 9, 2020 and updated July 25, 2021 without publication time limits on PubMed, Embase, CINHAL, Scopus, Cochrane Library, BioArchives, and OpenGrey.eu. Primary research on maternal gut microbiota in the postpartum (up to one year after childbirth) were eligible. Postpartum gut microbiota comparisons to pregnancy or non-pregnancy gut microbiota were of interest, therefore, studies examining these in addition to the postpartum were included. Studies were excluded if they were only conducted in animals, infants, pregnancy, or microbiome of other body locations (e.g., vaginal). Data extraction of microbial composition and diversity were completed and synthesized narratively. Studies were assessed for risk of bias. A total of 2512 articles were screened after deduplication and 27 were included in this review. Of the 27 included studies, 22 addressed the primary objective. Firmicutes was the predominant phylum in the early (<6 weeks) and late postpartum (6 weeks to 1 year). In early postpartum, *Bacteroides* was the predominant genus. Findings from longitudinal assessments

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2023.03.042.

of alpha and beta diversity from the early to the late postpartum varied. Nineteen of the 27 studies assessed biological and environmental factors influencing the postpartum gut microbial profile changes. Timing of delivery, probiotic supplementation, triclosan exposure, and certain diets influenced the postpartum gut microbiota. Regarding health conditions and intermediate clinical measures assessed in 8 studies; inflammatory bowel disease, postpartum depression, early-onset preeclampsia, gestational diabetes, excessive gestational weight gain, and anthropometric measures such as body mass index and waist-to-hip ratio were related to gut microbiota changes. There is limited data on the maternal postpartum gut microbiota and how it influences maternal health. We need to understand the postpartum maternal gut microbiome, establish how it differs from non-pregnancy and pregnancy states, and determine biological and environmental influencers. Future research of the gut microbiome's significance for the birthing parent in the postpartum could lead to a new understanding of how to improve maternal short and long-term health.

Keywords

Gut microbiome; Microbiome; Microflora; Maternal; Women; Postpartum

Introduction

Background

The gut microbiota is a collection of microorganisms inhabiting the intestinal tract, which play a key role across the lifespan in immunity, metabolism, and other health functions. [1] Thus, factors that influence the gut microbiota, such as pregnancy, are important research areas.

Pregnancy is characterized by immunological changes, such as elevated pro-inflammatory cytokines which cause low-grade inflammation. [2,57] Additionally, hormonal and metabolic adaptations occur to help sustain fetal and neonatal development. [1,60] These adaptations are associated with maternal gut microbiota changes from the first to the third trimester, such as reduced alpha diversity (richness), increased Actinobacteria and Proteobacteria abundance, decreased *Faecalibacterium* abundance, and increased beta diversity. [2–4].

The effects of pregnancy on gut microbiota are expected to continue during the postpartum period. The postpartum period is categorized into three phases: the initial phase occurs in the first 6–12 h after birth, the subacute phase follows up to six weeks and the delayed phase can last up to six months. [5,61] The initial phase is marked by rapid changes with possible crises, such as postpartum hemorrhage, while the subacute phase is characterized by slower changes, including genitourinary recovery and metabolic alterations. [5] The delayed postpartum phase involves gradual changes, for example, connective tissue restoration. [5] Other physiological changes after pregnancy (e.g. cardiovascular changes) occur for up to one year after childbirth. [6–7] Given the physiologic changes happening in the first year postpartum, there is biological plausibility that changes in the postpartum period could influence the maternal gut microbiota. However, many studies of the gut microbiota in this

period are focused on bacterial colonization of the newborn gut. [3,8–11] There is limited data on the maternal postpartum gut microbiota and how it influences maternal health.

Objectives

The primary objective of this paper was to synthesize the literature on the postpartum gut microbiome composition and diversity measured in stool samples from healthy mothers of predominantly term infants. The secondary objectives were (1) to identify biological and environmental factors that influence postpartum maternal gut microbiota and (2) to assess health conditions and clinical intermediate measures associated with postpartum gut microbiota changes in all mothers.

Materials/Methods

Our study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) on March 25, 2021 (registration number: 238390). The Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) statement guidelines were used for conducting and reporting study protocol. [12]

Eligibility Criteria, information Sources, search strategy

Electronic searches were conducted on PubMed, Embase, CINHAL, Scopus and Cochrane Library, BioArchives, OpenGrey.eu and hand selection of applicable journals/conference proceedings was used to find unpublished and grey literature. Searches were conducted on November 9, 2020 and updated on July 25, 2021. Controlled search was utilized with Boolean search operations and/or specific database search operations (e.g., MeSH). Search terms included keywords and controlled vocabulary in certain databases for the following: mothers, maternal, patient, microbiome, postpartum, pregnancy and prepartum. Human filter was applied with no restrictions on language, publication period or type. Search equations for each database are provided in Table 1. A hand search of references of relevant review articles was conducted to identify studies missing from electronic searches.

Study selection

Studies selected for this review were primary research on maternal gut microbiota in the postpartum period (up to one year after childbirth) that used quantitative data capture and analysis. Comparators or controls of pregnancy or non-pregnancy gut microbiota were of interest, therefore studies examining these in addition to the postpartum were included. No limits were made to study methods, interventions, or exposures. Studies were excluded if they were on animals, infants, the pregnancy period only, other microbiome locations (e.g., vaginal), or were secondary research.

Our study populations differed given our objectives. The study population for the primary objective are healthy mothers of predominantly term infants, and for the secondary objectives the study population are mothers regardless of their neonate’s gestational age at birth or their health status. For all objectives, gut microbiota outcomes included alpha or beta diversity and relative abundance (composition) at any taxonomy level and domain of life. Various indices measuring diversity were expected, such as Shannon’s for alpha

and Principal Coordinates Analysis (PCoA) for beta diversity. For the first secondary objective, different biological and environmental factors were eligible (e.g., maternal diet, medications, and environmental toxins) with exposure from pregnancy up to one year post-partum. For the other secondary objective, various maternal health conditions (e.g., postpartum depression) and clinical intermediate measures (e.g., anthropometric measures) were eligible.

Data extraction

From eligible studies, 20 were randomly chosen for pilot screening of abstracts by two reviewers (A.L.J. and W.W.) using the Rayyan screening platform. Cohen's kappa was calculated to interpret inter-rater reliability using the defined inclusion/exclusion criteria. The reviewers independently screened the remaining articles. Conflicts were resolved together without need for a tiebreaker. Once full text was retrieved (W.W.), 7 articles were randomly chosen to pilot full-text screening (L.K. and W.W.). Cohen's kappa was calculated to ensure inter-rater reliability. Once conflict was resolved, reviewers independently screened the rest without need for a tiebreaker. Initial and updated electronic search results, inclusions, and exclusions were recorded on a PRISMA diagram.

Data extraction utilized a standardized, pre-piloted form. Information extracted included: study setting and population, methodology, participant demographics, intervention and control conditions, recruitment and retention, measurement timepoints, outcomes including indices/scales used, and information used to assess risk of bias. Data was independently extracted by three authors (W.W., L.K., and J.S.) with need for an additional reviewer (A.L.J.) to resolve discrepancies. Any missing data were requested by contacting study author(s).

Assessment of risk of bias

Risk of bias assessment was completed by 2 authors (W.W. and L.K.). Cochrane's ROBINS-1 tool [13] was used for non-randomized studies and Cochrane's revised RoB 2 tool [14] was used for randomized controlled trials (RCTs). We piloted the tools on 2 randomly selected studies to check for consistency. Each reviewer then independently assessed risk of bias for each study. Discrepancies in judgement were resolved without need for a tiebreaker.

Data synthesis

Data were narratively synthesized and organized by review objective. Statistical analysis was not used because included studies were not sufficiently homogenous, with different studies reporting different interventions, comparators, and outcomes. When referring to the population of interest, terms used by included studies (i.e., "mother") were used in review synthesis instead of gender inclusive terms.

Results

Study selection and characteristics

There were 7952 records retrieved, 2512 remained after deduplication, and 27 included in this review (Fig. 1). Eighteen studies were observational of which 16 were cohort and 2 were case-control studies (Table 2). Eight were RCTs, [2,15–21] and 1 used open-label treatment without treatment randomization. [22] The 8 RCTs were registered on ClinicalTrials.gov, but only one registered prior to participant enrollment. [18] None of the RCTs were retracted. For included studies, sample size ranged from 4 to 253. Three studies used a relatively small sample size of 4–20, [23–25] while 7 studies included ≥ 100 postpartum women. [17,20–21,26–29] Studies varied in location, with 5 conducted in United States, [19,23,31,35,38] 2 in China, [32,36] 1 in Japan, [22] 1 in Kenya, [18] and 18 in European countries [2,15–17,20–21,24–30,33–34,37,39–40] (e.g., Norway [20–21,27,29, 33] and Spain [25,37].

Seventeen studies used 16S rRNA gene sequencing, [2,19,22–36] a widely used sequencing method. Other sequencing methods used were 16S rDNA in 3 studies, [18,37–38] and whole genome shotgun metagenomic sequencing in 3 studies (Table 2). [19,31,39] Regarding diversity findings relevant to our objectives, 3 studies assessed only alpha diversity, [18,24,29] 1 study assessed only beta diversity [2] and 15 studies assessed both alpha and beta diversity. [16,19–20,23,26–28,32–39] Of the studies using clustering analysis for beta diversity (N = 13), [2,16,19,23, 26–27,32–38] 12 used unsupervised approaches (Tables 3 and 4). [2,16,19,23,26–27,33–38] Since the previous literature review on this topic in 2017, [41] we included 12 additional studies in this review. [16,18,26,30,32,34–40].

Risk of bias of included studies

The Risk of Bias 2 (ROB 2) was used to assess the 8 RCTs, which categorized all as low risk of bias. Risk of Bias in Non-Randomized Studies- of Interventions (ROBINS-1) was used to assess the 18 observational studies and 1 open label study. The risk of bias was judged as low in 5 studies and moderate in 14 studies (Table 2).

Synthesis of results

Postpartum gut microbiome profile of healthy mothers—Of the 27 included studies, 22 analyzed the postpartum gut microbiome profile of healthy mothers of predominantly term infants (supplementary material). Thirteen of the 22 studies were primarily aimed to understand the maternal microbiome for the sake of infant. Nine studies assessed the early postpartum (<6 weeks), [2,15–17,24,27,31–32,38] 9 studies assessed the late postpartum (6 weeks − 12 months), [18–22,25,28,30] and 4 studies longitudinally assessed early to late postpartum [23,35,37,39] (Table 3). Regarding diversity findings, some studies analyzed diversity of the maternal gut microbiome in comparison to their infant's gut microbiome [20,25,28,31,35,38–39] or to microbiomes from other body sites (e.g., oral cavity) [31,35] or only looked at diversity of the infant's gut microbiome. [21] However, there were 4 longitudinal studies assessing early to late postpartum that analyzed diversity over time, [23,35,37,39] and there were 7 studies that compared diversity in pregnancy to postpartum. [2,16,24,26,28,32,39]

Early postpartum—In the studies of the early postpartum, 4 assessed phylum-level composition and reported Firmicutes as predominant. [24,27,31,38] Only 1 study assessed family-level and found high relative abundance of families belonging to Firmicutes, such as *Lachnospiraceae*. [24] Compositional analysis on the genus-level by 2 studies reported *Bacteroides* as predominant. [24,31] Other abundant genera reported include *Bifidobacterium*, [24,31] *Streptococcus*, [24] *Lactobacillus*, [24] *Faecalibacterium*, [24] *Roseburia*, [24] *Staphylococcus*, [24,31] *Prevotella,* [31] *Alloprevotella* [31] and *Escherichia*. [31] When the early postpartum period was assessed longitudinally, *Bacteroides* remained predominant after delivery and up to 4–6 weeks postpartum. [24,31] There were only 2 studies that assessed species-level composition, but only reported in percent prevalence. [15,17] In regards to diversity, Jost et al. looked over time in the early postpartum (4–6, 9–14, and 25–28 days) and found no changes in alpha diversity. [24]

Late postpartum—Six of the 9 studies assessing the late postpartum period analyzed phylum-level composition and all reported Firmicutes as predominant. [18–19,22,25,28,30] However, Ribado et al. found Bacteroidetes as the predominant phylum in 17 of 49 maternal samples. [19] Family-level composition was assessed in two studies. [18,25] Similar to the early postpartum, the most abundant families belonged to Firmicutes including *Lachnospiraceae*, *Clostridiaceae, Streptococcaceae,* and *Ruminococcaceae.* [18,25] *Ruminococcaceae* was found as predominant. [18,25] Another abundant family present in both studies was *Bifidobacteriaceae.* [18,25] On the genus-level, Butts et al. found *Bifidobacterium* as predominant and *Bacteroides* as subdominant while Hesla et al. found *Bacteroides* as predominant and *Bifidobacterium* as subdominant. [28,30] Few studies in the late postpartum period conducted species-level composition analysis. [20–21,25] Studies that investigated maternal probiotic supplementation focused on certain *Bifidobacterium* and *Lactobacillus* species. [21,25] In 1 probiotic study, placebo group fecal samples were analyzed for *B. animalis* subspecies *lactis*, *L. acidophilus* and *L. rhamnosus*, and found *L. acidophillus* as predominant. [21] Another study analyzed *B. animalis* subspecies *lactis,* along with species from *Bifidobacterium*, and found *B. longum* as predominant in the placebo group. [25] Schei et al. conducted a study on postpartum fungal mycobiome and found *Saccharomyces cerevisiae* as predominant, [20] similar to the Human Microbiome Project healthy adult cohort. [42]

Early through late postpartum—Of studies assessing early to late postpartum longitudinally, there were no significant changes in alpha diversity over time using Shannon's diversity (evenness and richness) index, [35,37,39] Simpson evenness, [35] or Pielou's evenness. [35] Cortes Martin et al. found that alpha diversity using the Chao1 richness index was significantly lower at 6 and 12 months postpartum compared to 3 weeks and 4 months (P <.05). [37] Studies which reported no differences only assessed up to 3 months [39] and 6 months [35] while Cortes-Martin et al. assessed up to 1 year postpartum. [37]

Regarding beta diversity, the maternal gut microbiome was stable at birth compared to 3 months postpartum using the Bray-Curtis dissimilarity index (P = 6.34e-08). [39] Williams et al. used Bray-Curtis dissimilarity matrix in nonmetric dimensional scaling plots and

PCoA for several timepoints (days 2, 5, and 10, and months 1, 2, 3, 4, 5, and 6), and also showed no significant differences. [35] The cohort used for this study was previously assessed by another study at the same timepoints without one participant, which also showed no differences in beta diversity by timepoint using Principal Component Analysis (PCA). [23] However, Cortes-Martin et al. using PCA found differences when comparing 3 weeks (T1) to 4–6 months (T2&T3) (P =.016) and 12 months (T4) (P =.08) postpartum. [37] Regarding composition analysis, there was increased abundance of Actinobacteria (P =.034) and decreased abundance of Verrucomicrobia (P =.034) and *Akkermansia* (P =.016) at T4 compared to T1. In the Archaea domain, decreased abundance of Euryarcheaota (P =.004) and *Methanobrevibacter* (P =.001) were noted at T4 compared to T1. [37]

Comparison to pregnancy or Non-Peripartum states—Nine studies analyzed the postpartum period in comparison with the third trimester of pregnancy. [2,16,20,22,24,26,28,32,39] Three of 4 studies that assessed phylum-level composition found Firmicutes as predominant in pregnancy and postpartum. [22,24,28] Conversely, Yassour et al. showed that Bacteroidetes and Firmicutes competed for predominance at several timepoints throughout pregnancy, birth and 3 months postpartum. [39] On the genus-level, Jost et al. found *Bacteroides* as predominant at 3–7 weeks before delivery and 4–6, 9–14 and 25–28 days postpartum. [24] Hesla et al. also found *Bacteroides* as predominant in the third trimester of pregnancy and 2 months postpartum. [28]

Five of the 6 studies assessing alpha diversity with Shannon's index did not show significant differences when comparing pregnancy to postpartum period (2–3 days-3 months). [16,24,28,32,39] No differences were found by Jost et al. with Chao1 index [24] or by Lv et al. with observed operational taxonomic units (OTUs), Faith's phylogenetic diversity or Pielou's evenness. [32] However, Crussell et al. showed a reduction with Shannon's diversity index (P =.012), microbial richness (P =.0002), and observed OTUs (P =.0002) from pregnancy to late postpartum (8 months), although no differences with Pielou's evenness index. [26]

Three studies compared postpartum gut microbiome beta diversity to pregnant or non-peripartum states. [2,26,28] Using Bray-Curtis Index of similarity, Hesla et al. found a high mean similarity between at 1 week before delivery and 2 months postpartum. [28] Another study reported a significant increase in weighted UniFrac (P =.005) and unweighted UniFrac distances (P =.001) at around 8 months postpartum compared to third trimester. [26] However, principal coordinate ordination showed these differences over time to reflect changes in individual bacterial community structure rather than a collective structural shift. [26] Koren et al. found a significant increase in beta diversity from the first to third trimester using weighted UniFrac distance ($P \leq 0.05$). [2] When compared to a healthy reference dataset of men and non-pregnant women from the Human Microbiome Project, [43] beta diversity in the third trimester was also higher. [2] This high beta diversity persisted to 3 weeks postpartum. [2] Apart from an indirect comparison by Koren et al., comparisons of the postpartum gut microbiota to the non-peripartum state were limited due to lack of a non-peripartum control group. [2]

Factors that influence maternal gut microbial changes in the postpartum period—Nineteen studies found various factors influencing postpartum gut microbial profile changes (Table 4). These included timing [27,40] and mode of delivery, [27,24–25] probiotic supplementation, [15–17,20–22] dietary intake, [23,33,37] breastfeeding status, [15,17–18,20–21, 28,30,35,37,24–25] environmental exposures, [19] and lifestyle. [28]

Preterm vs term delivery—Two studies assessed preterm delivery. [27,40] Dahl et al. compared spontaneous preterm and term deliveries and found Firmicutes phylum as predominant for both groups of mothers, but noted higher abundance of Firmicutes (P =.04) and lower abundance of Actinobacteria (P =.01) in preterm deliveries. [27] Morais et al. assessed preterm and extremely preterm deliveries without a comparison group of term deliveries, and also found Firmicutes as predominant. [40] On order-, family- and genus-levels, Dahl et al. found decreased abundances of OTUs belonging to *Bifidobacterium* and *Streptococcus* genera and Clostridiales order in the spontaneous preterm delivery group. [27] Morais et al. found *Bifidobacterium* genus as predominant in mothers of preterm and extremely preterm neonates. [40] Regarding diversity, Dahl et al. found that one interquartile range (IQR) increase in alpha diversity was associated with 48 % (95 %CI: 4.2 %,72 %) lower odds of preterm birth, but no differences in beta diversity. [27]

Mode of delivery—Two articles assessed the influence of delivery mode on the postpartum gut microbial profile. [23,30] One study found no significant differences in microbial composition between vaginal and cesarean births. [30] A sub-analysis by Carrothers et al. had similar composition findings and found no differences in alpha or beta diversity. [23]

Three studies included populations of only vaginal deliveries. [24–25,27] On the phylum-level, all showed Firmicutes as predominant. [24–25,27] Jost et al. and Turroni et al. analyzed lower taxa levels and found most bacterial groups with relatively high abundance belonged to the Firmicutes phylum (e.g., *Ruminococcaceae)*. [24–25]

Probiotic supplementation—Six studies explored probiotic supplementation's (second trimester – 3 months postpartum) influence on the maternal gut profile. [15–17,20–22] Two studies assessed supplementation of probiotic milk containing strains belonging to L. *acidophilus*, L. *rhamnosus* and B. *animalis* subsp *lactis* administered from 36 gestational weeks to 3 months postpartum. [20–21] Dotterud et al. observed increased relative abundance and prevalence of all 3 strains at 3 months postpartum in the probiotic group compared to placebo (P <.005). [21] Schei et al. analyzed the fungal mycobiome and found increased total fungal abundance (quantified by amount of fungal DNA copies) in the probiotic group compared to placebo at 3 months postpartum (P <.01). [20]

Gronlund et al. studied the effect of two different probiotic combinations supplemented from 2 months prior until 2 months after delivery compared to placebo. [15] One probiotic contained L. *rhamnosus* and B. *longum,* while the other contained L. *paracasei* and B. *longum*. [15] At 1 month postpartum, predetermined measures (colonization rates and fecal bacterial counts of *Bifidobacterium* genus, certain species of *Bifidobacterium* and *Clostridium*, A. *muciniphila*, and S. *aureus*) showed no differences between groups. [15]

Similarly, there were no differences between groups in *Bifidobacterium* diversity with the *bifidobacterium* diversity index. [15]

Enomoto et al. administered *Bifidobacterium* strains B. *breve* and B. *longum*, which belong to the Actinobacteria phylum, during the last month of pregnancy. [22] The open trial only found significant differences in the Proteobacteria phylum with lower abundances in the probiotic group compared to placebo at 4–18 months postpartum (P =.007). [22] Another trial focused on supplementation of L. *reuteri* during the last month of pregnancy and showed an increase in L. *reuteri* prevalence in the probiotic group compared to placebo at 1 month postpartum (P =.04). [17] Halkjaer et al. studied bacterial strains from *Bifidobacterium*, *Lactobacillus* and *Streptococcus* in an intervention trial using a multi-strain probiotic at 14–20 gestational weeks until delivery. [16] *Bifidobacterium* significantly increased over time from gestational weeks 14–20 until 2–3 days postdelivery in the probiotic group compared to placebo (P =.0388). [16] Beta diversity was significantly different between groups in the postpartum (P =.0014) and alpha diversity slightly increased with probiotic administration (P =.016). [16]

Dietary intake—Two studies assessed dietary intake. [23,33] Mandal et al. found that increased saturated fat intake was associated with decreased relative abundance of Firmicutes and Proteobacteria, [33] while Carrothers et al. found no association between increased saturated fat consumption and enrichment of *Bacteroides* and *Parabacteroides* as hypothesized. [23] Regarding nutrient and caloric rich diets, Carrothers et al. showed consumption of both were positively associated with relative abundance of Firmicutes and inversely associated with relative abundance of Bacteroidetes. [23] Both studies also assessed protein intake. One study found that increased protein intake was associated with increased *Methanobrevibacter* abundance, [33] while another found a significant association between increased intake and decreased *Spirochaetes* abundance ($P \leq 0.01$). [23] With regards to vitamin D, Mandal et al. found that higher intake was associated with reduced alpha diversity (P <.001), [33] and Carrothers et al. found a positive association between intake and *Dialister* abundance (P <.01). [23] Additionally, Carrothers et al. found significantly higher microbial evenness (alpha diversity) in women in the third quartile intake of vitamin B-12 compared to other quartiles (P <.05). [23]

Breastfeeding—Thirteen studies assessed the gut microbial profile of a general population of breastfeeding mothers, [15,17–18,20–21,28,30,35,37,24–25] but only 3 studies defined breastfeeding type (e.g., intensity or duration) of their study population. [23–24,35] Regarding breastfeeding duration, Carrothers et al. studied 20 women breastfeeding ≥5 months and Williams et al. studied the same cohort, with addition of one more mother, and both assessed the first 6 months postpartum. [23,35] Both studies found *Bacteroides* among the most abundant and beta diversity as unchanged over time, [23,35] and Williams et al. found no changes over time in alpha diversity. [35] Breastfeeding intensity was defined in a study population assessed by Jost et al., where the gut microbiome of 8 exclusively breastfeeding women at 1 month postpartum was similar to their gut microbiome in the third trimester. [24] None of these studies had a comparison group of individuals with different breastfeeding status.

Other factors—An environmental factor was assessed in only 1 study which looked at triclosan exposure, a chemical found in personal wash products at home. [19] Triclosan exposure increased abundance of species that are broadly antibiotic-resistant and belonged to Proteobacteria. Triclosan-resistant E. *coli* was the most enriched in the exposed group. [19] Microbial diversity decreased from 2 to 10 months postpartum with exposure but the difference was not significant. [19]

Hesla et al. studied anthroposophic lifestyle, which is characterized by increased fermented vegetable consumption, prolonged practices of breastfeeding, a stress-free environment, and more homebirths. [28] There were no significantly different gut microbial patterns between mothers of the anthroposophic and non-anthroposophic lifestyles. [28] Another study looked at secretor status phenotype, where mothers with a secretor phenotype have the functional α-1–2-fucosyltransferase enzyme to produce certain residual human milk oligosaccharides not found in non-secretor mothers. [18] There was no association between gut microbial composition of mothers based on secretor status phenotype, except for higher *Clostridium perfringens* abundance in non-secretor mothers (P =.028). [18] There were no significant changes in alpha diversity between secretor status. [18]

Maternal health conditions and intermediate clinical measures associated with gut microbiota changes—Eight studies investigated associations between postpartum maternal gut microbial profile changes and health conditions and/or clinical intermediate measures (Table 4). Health conditions and clinical intermediate measures studied were early-onset preeclampsia (early-PE), gestational diabetes (GDM), inflammatory bowel disease (IBD), overweight/obese (OW/OB) pre-pregnancy weight, and excessive gestational weight gain (GWG) and postpartum depression (PPD).

Maternal health conditions—One longitudinal study assessed early-PE. [32] At the genus level, there was enrichment of *Actinomyces* at 1 week postpartum and *Clostridium* at 6 weeks postpartum in mothers with early-PE compared to healthy controls. An unclassified species of *Streptococcus* was also found enriched in mothers with early-PE at 6 weeks postpartum. [32]

Decreased abundance of *Faecalibacterium* was observed in a study that analyzed PPD compared to healthy controls. *Faecalibacterium* was negatively associated with severity of depressive symptoms. [36] This study also showed PPD patients had increased abundance of bacteria belonging to the *Enterobacteriaceae* family, which is associated with intestinal inflammation. [36,44]

Another study utilizing 16S rRNA gene amplicon sequencing found that within the *Faecalibacterium* genus, some OTUs increased while others decreased at 8 months postpartum in women with previous GDM compared to women with a previous normoglycemic pregnancy. [26] This study also identified the Actinobacteria phylum and several subdominant taxa including *Collinsella* as taxonomic biomarkers of GDM. Depletion of *Bacteroides*, *Isobaculum* and *Clostridium IV* was observed in the third trimester of pregnancy and 8 months postpartum compared to healthy controls. [26]

One study on IBD from pre-pregnancy to the postpartum found that when comparing ulcerative colitis patients to Crohn's disease patients, ulcerative colitis patients had higher abundance of *Streptococcus, Bacteroides ovatus*, and an unclassified member of *Lachnospiraceae,* and Crohn's disease patients had higher *R. bromii*. [34]

Most studies did not find an association between the analyzed maternal health condition and gut microbial diversity changes. [26,32,34] One exception is the study on PPD, which reported significant increase in beta diversity in PPD mothers compared to healthy controls ($P = 2e^{-14}$). [36]

Clinical intermediate measures—Four studies assessed clinical intermediate measures in association with gut microbiota changes. [23,29–30,37] One study did not find significant changes in microbial composition based on BMI categories (normal, overweight, and obese). [30] However, 3 studies on BMI measures reported microbial profile changes. One study found a positive correlation between abundance of the *Clostridiaceae* family and certain anthropometric measures including current postpartum BMI, waist-to-hip ratio, waist circumference, and weight, while another study found a negative correlation between *Clostridiaceae* and overweight/obese (OW/OB) pre-pregnancy BMI. [29,37] One study found that increased abundance of the *Parabacteroides* genus was associated with increased current BMI measured at the postpartum study visit. [23] An oppositive trend was seen in another study with decreased *Parabacteroides* abundance associated with maternal OW/OB, but was not significant. However, the study did find a significant association between decreased *Parabacteroides* species OTU with maternal OW/OB. [29] Maternal OW/OB was also associated with lower alpha diversity and lower *Lachnospira,* unclassified *Christensenellaceae, Parabacteroides* sp., and *Bifidobacterium sp*. abundance. [29] Higher *Blautia* abundance was associated with excessive GWG, [29] while another study found lower *Blautia* abundance associated with increased waist circumference. [37]

When studying urolithin metabotypes, which are polyphenol metabolism profiles that may indirectly reflect an individuals' gut microbiome and possibly influence cardiometabolic health, the maternal gut microbiota showed characteristic changes based on the metabotype. [37] UM-B (metabotype B) showed higher postpartum energy metabolism and was positively associated with microbial groups Archaea, *Methanobrevibacter*, *Ellagibacter* and *Prevotella*. [37] Greater reductions in BMI and waist-to-hip ratio were found in UM-A, which was predominated by *Gordonibacter,* compared to UM-B. [37] Microbiota profiles of mothers with UM-B displayed higher alpha diversity compared to those with UM-A at 1 year postpartum (Shannon's diversity index, $P = .083$). [37]

Discussion

Principal findings

This review synthesizes findings on general composition and diversity of the gut microbiota profile of healthy women of predominantly term infants. In the early and late postpartum period, Firmicutes was the predominant phylum and *Bacteroides* was the predominant genus in the early postpartum. Changes in alpha and beta diversity were only reported after 4–6 months postpartum when compared to pregnancy or early postpartum. For alpha diversity,

changes were only observed with diversity estimators of microbial richness (i.e., Chao1 and observed OTUs).

We also synthesize findings on biological and environmental factors and clinical intermediate measures associated with gut microbial changes in all mothers in the postpartum. Regarding factors influencing microbial profiles, several microbial taxa were depleted and/or enriched based on delivery timing. No significant changes in microbial composition or diversity were noted with delivery mode. RCTs on probiotic supplementation showed depletion and/or enrichment of several genera and species compared to placebo groups. Dietary intake showed associations between increased consumption of fat-soluble vitamins, cholesterol, nutrient, calories, protein, and carbohydrates on enrichment and/or depletion of certain microbial taxa levels. In terms of environmental influences, triclosan exposure resulted in enrichment of species that are resistant to this chemical. Microbial profiles of mothers did not significantly differ based on secretor status phenotype or anthroposophic lifestyle.

Studies assessing maternal health conditions (early-PE, PPD, and GDM) all observed enrichment and/or depletion of various microbial taxa compared to healthy controls. Only 1 of 4 studies assessing various anthropometric measures did not find changes associated with microbial composition. Regarding maternal OW/OB and urolithin metabotype A, lower alpha diversity was seen.

Comparison with existing literature

Mutic et al. published in 2017 the only review on postpartum maternal microbiota. [41] It synthesized findings on biological, environmental, and maternal health influences on microbial changes. However, findings were limited since most included studies did not directly analyze the human postpartum maternal gut microbiota. [41] The only study included with a primary objective of studying the human postpartum maternal gut microbiota was authored by Koren et al. regarding GDM. [2] This study [2] was included in this systematic review along with new studies published after Mutic et al. [41] on associated health conditions and postpartum maternal microbiota changes.

Strengths and limitations

Previous research of the gut microbiota in the postpartum period is focused on neonatal microbial colonization. This is the first systematic review that focuses on the maternal gut microbiota. Inclusion of more studies on postpartum maternal human gut microbiota strengthens this review, compared to the previous review [41] where direct connections to human population were very limited. [41]

Although the studies in this review directly examined the population of interest (i.e., postpartum mothers), findings are limited by the narrative synthesis approach used. This approach was necessary due to the large study heterogeneity across all studies. Included studies differed in study population, sample size and study design. Studies also varied in methods of DNA sequencing, where certain primers have been found to bias composition and diversity analysis. [2,58,59] Different sub-regions of 16S rRNA sequencing are poor

at classifying certain microbial taxa, such as V1-V2 with sequences of *Proteobacteria*. [45] Studies in this review sequenced various sub-regions, which also contribute to the large study heterogeneity and limits the synthesized findings. Some studies performed OTU level analysis based on 16S rRNA gene amplicon sequencing data, however, OTU level analysis is most reliably addressed with shotgun metagenomic sequencing or targeted qPCR.

There are various combinations of distance measures and algorithms, [46] and because there is not one standard pipeline approach to clustering, [46] use of varied combinations may lead to differences in clustering performance. [46–48] Additionally, clustering methods (supervised or unsupervised) [49] could contribute to differences in study findings, however, most of the relevant studies in our review (Tables 3 and 4) used unsupervised clustering approaches.

Conclusion

Inconsistent findings in some areas of the addressed review objectives left unanswered questions about the reason for variability. Most differences in competing findings seen across the addressed review objectives were limited by study population and methodology heterogeneity. Larger sample size and use of DNA sequencing with universal primers, similar sub-regions and gene depth sequencing criteria that do not bias against certain bacterial taxa would be important future research. Analysis of other domains of microbes (archaea, fungi, protozoa, and viruses) and all taxa levels should be encouraged. Furthermore, functional associations between species-level composition and maternal health are valuable.

There is a need to understand the postpartum maternal gut microbiome for the mother's sake. We need to establish how it differs from non-pregnancy and pregnancy states and determine biological and environmental factors that influence the maternal gut microbiota during postpartum. Further studies which include a healthy non-peripartum group for comparison could be especially useful.

Important research questions include: does the gut microbiota return to pre-pregnant states? If so, when does the gut microbiota return to pre-pregnant state? What practices or exposures during pregnancy or post-partum ensure a healthy postpartum microbiota profile? What factors influence the transition back to pre-pregnant state? And how does the transition or lack of transition influence the health of the mother, infant, and subsequent pregnancies? Further research of the gut microbiota's significance during this period could lead to new understanding of how to improve maternal and child health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

BMI	Body Mass Index

CINAHL	Cumulative Index to Nursing and Allied Health Literature
early-PE	early onset pre-eclampsia
GDM	gestational diabetes mellitus
GWG	gestational weight gain
IBD	inflammatory bowel syndrome
MeSH	Medical Subject Headings
OTUs	operational taxonomic unit
OW/OB	overweight/obese
PCA	Principal Component analysis
PCoA	Principal Coordinate analysis
PPD	postpartum depression
PRISMA	Preferred Reporting Items for Systematic Reviews and meta-Analyses
RCTs	Randomized controlled trials
ROBINS	Risk Of Bias In Non-Randomized Studies – of Interventions
RoB 2	Risk of Bias for Randomized Trials
UM-A	Urolithin Metabotype A
UM-B	Urolithin Metabotype B

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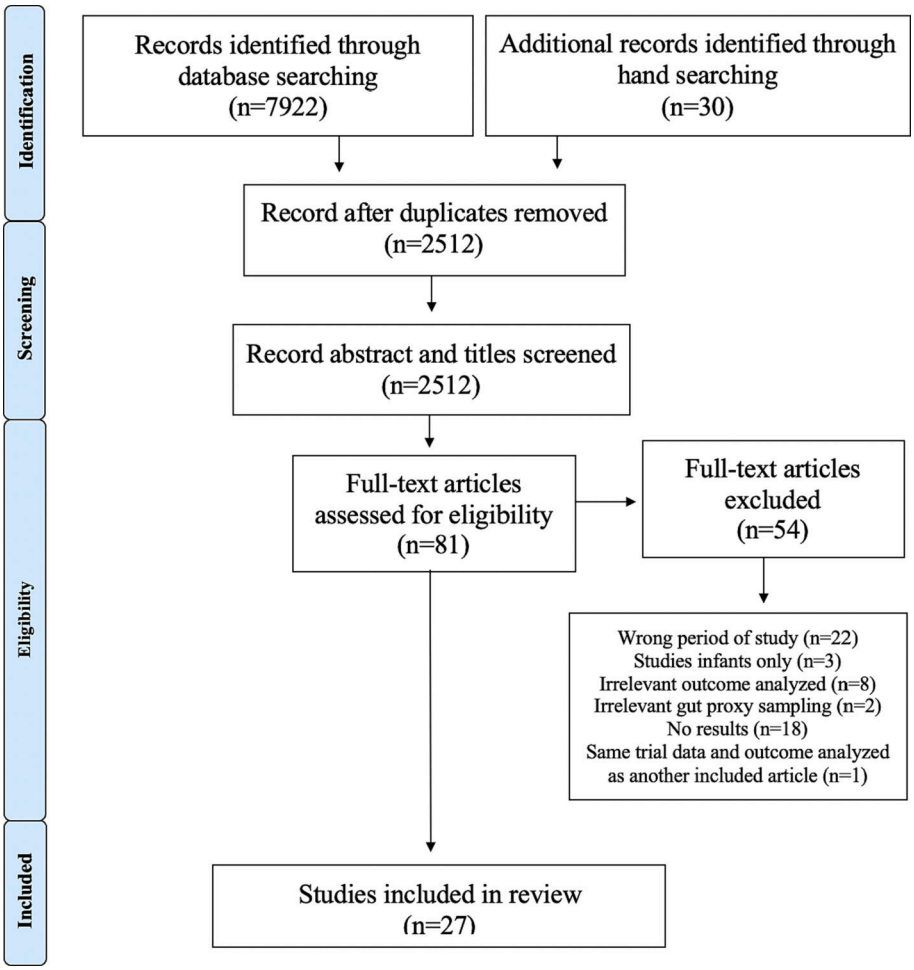

Fig. 1.

PRISMA flow diagram: summary of record searches and selections Arrows depict flow of records through each stage. Number of records in each stage is represented by (n=#). PRISMA, Preferred Reporting Items for Systematic Review and meta-Analyses *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *m*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097.

Table 1

Full Search Equations Used in Each Database.

Database	Search Equation
Scopus	(TITLE-ABS-KEY (maternal OR mother OR mothers OR patient) AND (TITLE-ABS-KEY (microbiome OR microbiota)) AND (TITLE-ABS-KEY (pregnancy OR postpartum OR prepartum OR pregnant)) AND (LIMIT-TO (EXACTKEYWORD, “Human”) OR LIMIT TO (EXACTKEYWORD, “Humans”))
Cochrane Library	#1: MeSH descriptor: [Mothers] explode all trees #2: maternal OR Mother OR Mothers OR Patient #3: #1 AND #2 #4: MeSH descriptor: [Microbiota] explode all trees #5: Microbiome OR Microbiota #6: #4 AND #5 #7: MeSH descriptor: [Postpartum Period] explode all trees #8: MeSH descriptor: [Pregnancy] explode all trees #9: Pregnancy OR postpartum OR prepartum OR Pregnant #10: #7 AND #8 AND #9 #11: #3 AND #6 AND #10
CINAHL	#1: (MH “Mothers+”)#2: (MH “Mothers+”) OR maternal OR Mother OR Mothers OR Patient#3: (MH “Microbiota+”)#4: (MH “Microbiota+”) OR Microbiome OR Microbiota#5: (MH “Pregnancy+”)#6: (MH “Postnatal Period+”) #7: Pregnancy OR postpartum OR prepartum OR Pregnant OR (MH “Postnatal Period+”) OR (MH “Pregnancy+”)#8: Pregnancy OR postpartum OR prepartum OR Pregnant OR (MH “Postnatal Period+”) OR (MH “Pregnancy+”)#9: Pregnancy OR postpartum OR prepartum OR Pregnant OR (MH “Postnatal Period+”) OR (MH “Pregnancy+”) AND (#2 AND #4 AND #8) #10: AB (#2 AND #4 AND #8) OR TI (#2 AND #4 AND #9)
PubMed	((“Mothers”[Mesh]) OR (maternal[tiab] OR Mother[tiab] OR Mothers[tiab] OR Patient[tiab])) AND (((“Microbiota”[Mesh] OR Microbiome[tiab] OR Microbiota[tiab]) AND ((Pregnancy [tiab] OR postpartum[tiab] OR prepartum[tiab] OR Pregnant [tiab] OR “Postpartum Period”[Mesh] OR “Pregnancy”[Mesh])))) AND (humans[Filter])
BioArchives	(((maternal OR Mother OR Mothers OR Patient)) AND (((Microbiome OR Microbiota) AND ((Pregnancy OR postpartum OR prepartum]))))
Embase	#1:’mother’:ab,ti OR ’maternal’/exp OR maternal:ab,ti OR ’mother’/exp OR mother:ab,ti OR ’mothers’/exp OR mothers:ab,ti OR ’patient’/exp OR patient:ab,ti#2: ’microflora’/exp OR microbiome:ab,ti OR microbiota:ab,ti #3: pregnancy:ab,ti OR postpartum:ab,ti ORprepartum:ab,ti OR pregnant:ab,ti OR ’pregnancy’/exp #4: #1 AND #2 AND #3 AND [humans]/lim

Table above displays the full search equations used specifically for each selected database. Separate numbered lines indicate separate search lines used when applicable.

Table 2

Summary of Included Studies.

First author, year (country)	Study Type	Study Population	Inclusion Criteria	Exclusion Criteria	SR Aim (s)	Microbial Analysis	ROB Tool & ROB Assessment
Abrahamsson et al., 2009 (Sweden) [17]	Double-blind RCT	232 mothers enrolled at gest wk 35 (probiotic group (N = 95) and placebo group (N = 93) completed the study) [50]	At least 1 family member with allergic disease	Infants that required neonatal care	1, 2a	culture (*L. reuteri* and *Lactobacillus*)	RoB-2: low
Butts et al., 2020 (New Zealand) [30]	Longitudinal Cohort	78 BF mothers of different ethnicities (NZ European (N = 53), Asian (N = 8), Maori and Pacific Island (N = 17)) (BMI normal (N = 27), overweight (N = 31), obese (N = 20)) (vaginal (N = 63) cesarean (N = 14)) [51]	EBF or primarily BF with ≤2 formula feeds/day (aged 18–55) and permanent residence in Manawatu–Wanganu region	Preterm birth, infants that required neonatal care, clinically significant biliary, cardiac, endocrine, hematologic, hepatic, neurological, pancreatic, pulmonary, mental disorders in medical hx, active dieting.	1, 2a, 2b	16S rRNA (V3-V4)	ROBINS-1: moderate
Carrothers et al., 2015 (USA) [23]	Longitudinal Cohort	20 healthy women (all EBF for ≥ 4 mo) (vaginal (N = 16) cesarean (N = 4))	18 yrs or older and planning to BF	–	1, 2a, 2b	16S rRNA (V1-V3)	ROBINS-1: moderate
Chu et al., 2017 (United States) [31]	Longitudinal cohort; matched cross-sectional cohort	157 dyads at delivery from both cohorts (N = 60 dyads sampled in PP longitudinally)	Pregnancy at > 28 gest wks), ≥ 18 yrs of age, willing to consent to protocol	HIV or Hepatitis C infection, immunosuppressive disease, cytokine/immunosuppressive agent use within previous 6 mo, cancer hx (except squamous/ basal skin cell carcinoma managed with local excision, treatment of suspicion of ever having toxic shock syndrome, major gastrointestinal surgeries (except cholecystectomy/ appendectomy) in last 5 yrs	1	16S rRNA (V5-V3), whole-genome shotgun metagenomic sequencing	ROBINS-1: moderate
Cortes-martin et al., 2019 (Spain) [37]	Longitudinal Cohort	40 healthy women recruited 1 wk PP (vaginal (N = 28) and cesarean (N = 12)) delivery of healthy BF infants)	Healthy women delivering a healthy baby and BF in neonatal period	Dietary supplementation (prebiotic and probiotic supplements) and drug administration (abx) 1 yr PP	1, 2b	16S rDNA	ROBINS-1: moderate
Crusell et a.L, 2018 (Denmark) [26]	Longitudinal Cohort	213 mothers enrolled in third trimester (GDM (N = 50) and non-GDM (N = 161)) of which 125 were assessed in PP (previous GDM (N = 43) and non-GDM (N = 79))	Singleton pregnancy, of Danish white origin, without preeclampsia at the time of enrollment, and multiparous with a previous normoglycemic pregnancy	Abx within 2 mo before first visit	1, 2b	16S rRNA (V1-V2)	ROBINS-1: low
Dahl et al., 2017 (Norway) [27]	Case-control	121 PP mothers of term (N = 102) and preterm (N = 19) vaginal delivery [from Norwegian Microbiota Study (NoMIC)] [52]	Fluent in Norwegian, residence in Eastern Norway	Abx use on or after birth	1, 2a	16S rRNA (V4)	ROBINS-1: moderate

First author, year (country)	Study Type	Study Population	Inclusion Criteria	Exclusion Criteria	SR Aim (s)	Microbial Analysis	ROB Tool & ROB Assessment
Dotterud et al., 2015 (Norway) [21]	Double-blind RCT	415 enrolled pregnant mothers; samples analyzed: probiotic group (N = 111 in pregnancy, N = 116 at 3 mo PP) and placebo group (N = 120 in pregnancy, N = 124 at 3 mo PP)[from Prevention of Allergy Among Children in Trondheim (PACT) study] [53]	Pregnant women > 36 gest wks, understood Norwegian, signed written form for consent, planning to BF in first 3 mo PP, liked/tolerated fermented milk, not at risk of pregnancy complications	Took probiotic supplements in last 4 wks, plan to move away from Trondheim < 25 mo after randomization	1, 2a	qPCR	RoB-2: low
Enomoto et al., 2014 (Japan) [22]	Open-label, non-RCT	166 enrolled mothers; probiotic group (N = 130 at baseline, N = 49 analyzed in PP) and control group (N = 36 at baseline, N = 15 analyzed in PP)	Pregnant women	Severe hepatic dysfunction, renal and respiratory dysfunction, cardiovascular disorders, endocrine disorders, metabolic dysfunction, habitual ingestion of probiotics	1, 2a	16S rRNA (V6-V8)	ROBINS-1: moderate
Gronlund et al., 2011 (Finland) [15]	Double-blind RCT	80 PP dyads with L. *rhamnosus* and B. *longum* supplementation (N = 29 dyads), L. *paracasei* and B. *longum* supplementation (N = 29 dyads) or placebo (N = 22 dyads)	Clinical sx of allergy with reactivity proven by prick-test against the allergen, EBF ≥ 4 mo and partial/exclusive BF continued until 6 mo of infancy, high risk allergy families		1, 2a	qPCR	RoB-2: low
Halkjaer et al., 2020 (Denmark) [16]	Double-blind, RCT	50 obese nulliparous women enrolled and randomized to placebo (N = 25) and probiotic (N = 25) (analyzed in PP: from placebo (N = 24) and probiotic group (N = 24))	Nulliparous singleton pregnant women with BMI ≥ 30 and < 35 kg/m2, ≥18 yrs old, normal nuchal translucency, read and speak Danish, consent to complete OGTT at 14–20 gest wks	>20 wk gest; pregestational diabetes or other serious diseases; previous bariatric surgery; probiotics use within the last mo before inclusion; probiotics use during the study intervention period other than the study provided probiotics; alcohol or drug abuse	1, 2a	SSU rRNA	RoB-2: low
Hesla et al., 2014 (Sweden) [28]	Longitudinal Cohort	116 PP mothers of anthroposophic (N = 51) and non-anthroposophic lifestyles (N = 65)[from the ALADDIN cohort] [54]	[From the ALADDIN cohort]	Infants born prior to 36 gest wks or miscarriage	1, 2a	16S rRNA (V3-V4)	ROBINS-1: low
Jost et al., 2014 (Switzerland) [24]	Longitudinal Cohort	7 healthy mothers delivering vaginally and EBF	EBF	Preterm and/or caesarean delivery, formula feeding, any variables affecting maternal microbiota, dietary supplementation and medication use during lactation and ≥ 4 mo prepartum	1, 2a	16S rRNA gene (V5-V6), qPCR	ROBINS-1: moderate
Koren et al., 2012 (Finland) [2]	RCT	91 pregnant women [55]	< 17 gest wks	History of metabolic or chronic diseases	1	16S rRNA (V1-V2)	RoB-2: low
Lv et al., 2019 (China) [32]	Longitudinal Cohort	150 singleton pregnant women with live birth including those with newly diagnosed PE in third trimester (N = 78 enrolled; 35 at 1 wk PP, 18 at 6 wks PP) and normotensive controls (N = 72	Cesarean deliveries	Comorbidities, multiple pregnancies, GDM, chronic hypertension	1, 2b	16S rRNA (V4)	ROBINS-1: moderate

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First author, year (country)	Study Type	Study Population	Inclusion Criteria	Exclusion Criteria	SR Aim (s)	Microbial Analysis	ROB Tool & ROB Assessment
		enrolled; 17 at 1 wk PP, 11 at 6 wks PP)					
Mandal et al., 2016 (Norway) [33]	Case-control	60 PP mothers[from the NoMIC] [52]	Prospective dietary intake information collected	–	2a	16S rRNA (V4)	ROBINS-1: low
Maqsood et al., 2019 (USA) [38]	Longitudinal Cohort	28 mothers [56 infants (28 pairs of twins)] [56]	Pregnant with twins	–	1	16S rDNA (V4)	ROBINS-1: moderate
Morais et al., 2020 (Portugal) [40]	Longitudinal Cohort	93 mothers of preterm infants (N = 117)	Preterm neonates and very preterm neonates (<32 wks gest age) hospitalized in NICU	–	2a	qPCR	ROBINS-1: moderate
Pagnini et al., 2019 (Kenya) [18]	Double-blind RCT	75 BF Kenyan mothers (PP fecal samples analyzed: N = 66)	Mothers of healthy infants 6.5–9.5 mos of age with hemoglobin > 70 g/L, Z-scores weight-for-age and weight-for-length > – 3	Inadequate fecal and/or breast milk sample collection, mothers of infants who received vitamin or mineral supplements 8 wks or abx 10 wks prior to study	1, 2a	16S rDNA (V3-V4)	RoB-2: low
Ribado et al., 2017 (USA) [19]	RCT	39 households with 26 completed sampling for all three timepoints; households randomized to triclosan and triclocarban (TC) exposure (N = 17) or no TC (N = 22)	Mothers who spoke/read English or Spanish, 18–42 yrs, low-risk singleton pregnancy of > 36 gest wks, no GDM or other endocrine conditions, willing to provide biological samples and medical record access of herself/infant, intention to remain in study area for next 15 mo, at least 5 of 6 expected stool samples available from household	–	1, 2a	16S rRNA (V4), whole-genome shotgun metagenomic sequencing	RoB-2: low
Schei et al., 2017 (Norway) [20]	Prospective cohort, RCT	298 dyads, where pregnant (N = 248) and PP (N = 253) mothers' fecal samples were analyzed); randomized to probiotic or heat-treated fermented skimmed milk with no probiotic from 36 gest wks until 3 mo PP [from the Pro-PACT Study] [21]	Pregnant women > 36 gest wks, understood Norwegian, signed written form for consent, planning to BF in first 3 mo PP, liked/tolerated fermented milk, not at risk of pregnancy complications; at least one pair of fecal samples from mother and offspring from Pro-PACT Study	Took probiotic supplements in last 4 wks, plan to move away from Trondheim < 25 mo after randomization	1, 2a	18S rRNA gene lTS1 region	RoB-2: low
Stanislawski et al., 2017 (Norway) [29]	Longitudinal Cohort	169 PP women comparing pre-pregnancy BMI groups: overweight/obese (OW/OB) (N = 117), non-OW/OB (N = 52) and comparing GWG groups (N = 116): low (N = 12), adequate (N = 41), excessive (N = 63) [from NoMIC] [52]	Provided a fecal sample, sample with high quality Illumina data, and height and pre-pregnancy weight were available to calculate BMI	Women missing gest weight gain, not full-term pregnancies, multiple gestation	2b	16S rRNA (V4)	ROBINS-1: moderate
Turroni et al., 2012 (Italy, Ireland, Spain) [25]	Prospective Cohort	11 infants of which 4 dyads were available (of dyads: all were vaginal	Healthy mothers, no abx or probiotic use in previous 3 mo	–	1, 2a	16S rRNA (V6-V8)	ROBINS-1: moderate

First author, year (country)	Study Type	Study Population	Inclusion Criteria	Exclusion Criteria	SR Aim (s)	Microbial Analysis	ROB Tool & ROB Assessment
		deliveries, BF (N = 3), and both BF and bottle-fed (N = 1))					
Van der Giessen et al., 2020 (Netherlands) [34]	Longitudinal Cohort	225 pregnant women enrolled with IBD (N = 46, of which had CD (N = 31) or UC (N = 15)) and healthy control (N = 179); with only 19 IBD, 13 CD and 6 healthy control samples analyzed in PP	IBD diagnosis, CD and UC based on HBI and SCCAI scoring	Unable to provide consent	2b	16S rRNA (V4)	ROBINS-1: moderate
Williams et al., 2019 (USA) [35]	Longitudinal Cohort	21 healthy BF women [23]	≥18 yrs old and planned to BF ≥ 6 mo	–	1, 2a	16S rRNA (V1-V3)	ROBINS-1: moderate
Yassour et al., 2018 (Finland) [39]	Paired-longitudinal cohort	44 families of which some PP samples from mothers were analyzed (N = 33)	Eligible human leukocyte antigen (HLA) genotype of the newborn conferring increased risk for type 1 diabetes	An older sibling enrolled, multiple gest, parents unwilling or unable to feed the infant with cow's milk-based products, < 35 wks gest at birth; technical challenges to participate; no HLA sample obtained before the age of 8 dys	1	whole-genome shotgun metagenomic sequencing, qPCR	ROBINS-1: low
Zhou et al., 2020 (China) [36]	Prospective Cohort	N = 57 PP mothers of which had PPD (N = 39) compared to healthy controls (N = 18)	20–49 years old, PPD diagnosis,17- Hamilton depression rating scale (HAMD) score is 7–24, disease onset after delivery is within 1 yr	Bipolar disorder/other serious mental disorder, dysnoesia, pregnancy, score > 2 on "suicide" item of 17-HAMD, previous suicide attempt within 1 yr, anorexia nervosa	2b	16S rRNA (V4)	ROBINS-1: low (NI) *

Table above displays (from left to right): summary of studies. Systematic review (SR) aim depicts which studies pertained to our study aims (1: gut microbial profile of healthy birthers of term infants, 2a: biological/environmental factors influencing gut microbial changes in all birthers in the postpartum, 2b: health conditions/clinical intermediate measures associated with gut microbial changes of all birthers in the postpartum).

Last column with risk of bias (ROB) tool used also shows ROB judgement which ranges from ROBINS-1: Low, Moderate, Serious, Critical, NI and in RoB 2: Low, High, Some Concerns.

Study methodology referring to previous published from authors of included study.

* Guidelines require overall ROB judgement to be assessed even though "NI" was concluded by both reviewers, therefore second assessment as 'moderate' was concluded by both.

Abx, antibiotic(s), BF, breastfeeding/breastfed, BMI, body mass index, CD, Crohn's disease, DNA, deoxyribonucleic acid, Dy(s), day(s), EBF, exclusive breastfeeding/breastfed, GDM, gestational diabetes mellitus, Gest, gestation/gestational, IBD, inflammatory bowel disease, Mo, month(s), NI, no information, PCR, Polymerase chain reaction, PE, preeclampsia, PP, postpartum, PPD, postpartum depressive disorder, qPCR, real-time polymerase chain reaction, rRNA, ribosomal ribonucleic acid, RoB-2, risk-of-bias tool for randomized trials, ROBINS-1, Risk Of Bias In Non-randomized Studies - of Intervention, UC, ulcerative colitis, Weeks, wks, Yr, year.

Table 3

Postpartum Gut Microbial Profile of Healthy Birthers of Term Infants.

First author	Times points measured			Comp*	Diversity	Major Findings:
	Pregnancy	Early PP	Late PP			
Abrahamsson et al. [17]	35 gest wk	1 wk	–	species	–	Prevalence of *L. retueri* was 85 % and prevalence of any Lactobacilli population was 85 % at 1 wk PP. *L. reuteri* prevalence was significantly higher from 35 gest wk – 1 wk PP.
Butts et al. [30]	–	–	6–8 wks	phylum, genus	–	Firmicutes was the predominant phylum. On the genus level, *Bifidobacterium* was predominant and *Bacteroides* was subdominant. Prevalent bacteria for all ethnic groups were *Ruminococcaceae, Bacteroides* and *Lachnospiraceae*.
Carrothers et al. [23]	–	2,5,10 d; 1 mo	2,3,4,5,6 mo	phylum, genus	alpha & beta	Firmicutes and *Bacteroides* were the most abundant phylum and genus, respectively. Alpha diversity did not change over time. Using PCA, there were no differences in beta diversity by timepoints.
Chu et al. [31]	early 3rd trimester	delivery& 4–6 wks		phylum, genus	–	Firmicutes was the predominant phylum in maternal stool. *Bacteroides* was prevalent and highly specific for the maternal stool with avg. abundance 27.8 %, IndVal = 0.943. *Bacteroides* was predominant after delivery and up to 4–6 weeks postpartum. Other abundant genera included *Bifidobacterium, Staphylococcus, Prevotella, Alloprevotella,* and *Escherichia*.
Cortes-martin et al. [37]	–	3 wks	4,6,12 mo	phylum, genus, family, class	alpha & beta †	There was increased abundance of Actinobacteria (P = 0.034) and decreased abundance of Verrucomicrobia (P = 0.034) and *Akkermansia* (0.016) at 12 mos compared to 3 wks PP. In the Archaea domain, decreased abundance of Euryarcheaota (P = 0.004) and *Methanobrevibacter* (P = 0.001) were noted at 12 mos compared to 3 wks PP. Total bacteria (p = 0.035) was increased at 12 mos compared to 3 wks PP. Using the Shannon's diversity index for alpha diversity, there were no significant changes over the PP period. Using the Chao1 richness index, alpha diversity was significantly lower at 6 and 12 mos PP when compared to 3 wks and 4 mos (P < 0.05). Using principal component analysis, there were significant differences in beta diversity when comparing 3 wks to 4–6 mo (P = 0.016) and 12 mo PP (P = 0.08).
Crusell et al. [26]	28.4 +/− 1.1 gest wks	–	~ 8 mo	phylum, class, order, family, genus	alpha & beta †	Alpha diversity was significantly increased with Shannon's diversity index (P = 0.012) and Observed OTUs (P = 0.0002), but not with Pielou's evenness and beta diversity was significantly decreased (P = 0.001) in pregnancy compared to PP.
Dahl et al. [27]	–	4 d	–	phylum	–	Firmicutes was the predominant phylum and at subdominant levels were Bacteroidetes and Actinobacteria.
Dotterud et al. [21]	30–36 gest wks	–	3 mo	species	–	In the placebo group, *L. acidophillus* was found as the predominant species. Prevalence and relative abundance of L. *acidophilus* La-5, L. *rhamnosus* GG, and B. *animalis* did not significantly change when comparing pregnancy to PP periods in the placebo group.
Enomoto et al. [22]	3 wks before delivery	–	~ 4–18 mo	phylum	–	Firmicutes was the predominant phylum. Significantly increased proportions of Actinobacteria in the microbiota of mothers at PP compared to pregnancy.
Gronlund et al. [15]	–	1 mo	–	–	bifidobacterium diversity	The median (interquartile range, IQR) bifidobacterial diversity index (DI) was 50 % (28.6 %–57.1 %) in mothers 1 mo PP. In maternal samples at 1 mo PP, the prevalence of samples with *Bifidobacterium* genus was 100 % including 98.7 % B. *longum*. *Clostridium coccoides* group was 100 % prevalent and *Akkermansia muciniphilla* was 85.3 % prevalent in maternal samples.

First author	Times points measured			Comp*	Diversity	Major Findings:
	Pregnancy	Early PP	Late PP			
Halkjaer et al. [16]	14–20, 27–30, 36–37 gest wks	2–3 d	–	genus, species	alpha	Relative abundance of *Lactobacillus* lower in baseline than PP (P = 0.02). *Bifidobacterium* nominally increases over time in the placebo group, but no significant difference between sample times for *Bifidobacterium*, *Lactobacillus* or S. *salivarius*. No significant differences in alpha diversity in pregnancy compared to PP.
Hesla et al. [28]	1 wk before delivery	–	2 mo	phylum, genus	alpha, beta	Firmicutes was the predominant phylum before and after delivery. Clostridiales and *Bacteroides* were predominant after delivery, while *Bifidobacterium* was subdominant after delivery. Mean Shannon index remained similar between samples before and after birth between all samples. There was high mean similarity with Bray Curtis index of similarity between pregnancy and PP samples.
Jost et al. [24]	3–7 wks before delivery	4–6, 9–14, & 25–28 d	–	phylum, family, genus	alpha	Firmicutes was the predominant phylum. There was high abundance of families belonging to Firmicutes including *Lachnospiraceae* which was predominant and *Ruminococcaceae. Bacteroides* was the predominant genus and remained predominant after delivery until 28 d postpartum. Other abundant genera included *Bifidobacterium, Streptococcus, Lactobacillus, Faecalibacterium, Roseburia,* and *Staphylococcus*. There were no significant changes in bacterial abundance over the perinatal period. *Streptococcus* decreased numerically over the PP, without significance. Alpha diversity did not significantly change over time between pregnancy and PP timepoints.
Koren et al. [2]	T1 (13.84 +/− 0.16 gest wks) and T3 (33.72 +/− 0.12 gest wks)	1 mo	–	phyla, genus, species	beta †	High levels of beta diversity in third trimester persisted for women 1 mth PP. Relative abundance of *Streptococcus,* is significantly enriched in 3rd trimester and 1 mo PP samples compared to 1st trimester is in highest abundance in 1 mo PP.
Lv et al. [32]	39.8 +/− 1.3 gest wks	1wk & 6 wks		genus, species	alpha	No significant differences in alpha diversity between antepartum and PP samples in healthy non-PE group (P > 0.05 for all diversity indexes). Microbial composition: samples at both 1 and 6 wks PP were highly consistent with samples at antepartum (P < 0.05 for two comparisons).
Maqsood et al. [38]	–	− 360 to 1680 hrs after birth	–	phylum	alpha & beta †	Firmicutes was the most abundant phylum. Bacteroidetes, Actinobacteria, and Proteobacteria were found as subdominant phyla.
Paganini et al. [18]	–	–	7.2 mo (avg baseline), 3 & 4 mo after	phylum, family, genus	–	At baseline in secretor and non-secretor mothers, gut microbiota was composed of Actinobacteria (8.9 % of the 16S rDNA reads), Firmicutes (73.7 %), Bacteroidetes (12.6 %) and Proteobacteria (3.6 %). The most predominant phylum was Firmicutes, and the most predominant family was *Ruminococcaceae*. Other abundant families included *Lachnospiraceae, Clostridiaceae, Streptococcaceae,* and *Bifidobacteriaceae.*
Ribado et al. [19]	–		2, 6, 10 mo	phylum, genus, species	alpha, beta †	Firmicutes was the pre-dominant phylum in 32/49 maternal samples and Bacteriodetes was the predominant phylum in 17/49 maternal samples.
Schei et al. [20]	35–38 gest wks	–	3 mo	species	alpha & beta	*Saccharomyces cerevisiae* was the predominant species in the maternal fungal mycobiome. Mothers had a higher alpha and beta diversity in pregnancy than PP, however the difference was not significantly different. Fungal abundance was significantly lower in PP vs pregnant women (P < 0.001).
Turroni et al. [25]	–	–	3 mo	phylum, family, species	–	Firmicutes was the predominant phylum with lower levels of detected Bacteroidetes. On the family level, *Ruminococcaceae* was predominant. Other abundant families included *Lachnospiraceae, Clostridiaceae, Streptococcaceae,* and *Bifidobacteriaceae*. In the placebo group, B. *longum* and B. *adolescentis* were the predominant species,

First author	Times points measured			Comp*	Diversity	Major Findings:
	Pregnancy	Early PP	Late PP			
						constituting 38.2 % and 20.3 %, respectively, of the sequences that were assigned to the genus *Bifidobacterium*.
Williams et al. [35]**	–	2,5,10 d; 1 mo	2,3,4,5,6 mo	phylum, genus	alpha & beta †	Most abundant genus was *Bacteroides* (22.9 +/− 1.3 %). There were no changes across time for alpha diversity (Shannon's diversity, Simpson evenness, and Pielou's evenness) of maternal fecal samples. Using Bray-Curtis dissimilarity matrix in nonmetric dimensional scaling plots and principal coordinate analysis, no significant differences in beta diversity were observed over time.
Yassour et al. [39]	27 gest wk	delivery	3 mo	phylum, species	alpha & beta	Mothers had a higher fraction of *Bacteroidetes* and *Firmicutes*. Maternal samples contained 20 or more species above 1 % relative abundance. There were no differences in alpha diversity from pregnancy to postpartum using the Shannon's diversity index. The maternal microbial communities displayed stability with significant overlap in the species-level composition between time points relative to random subject pairings (P = 2.82e-11, 6.34e-08, calculated with *t*-test) using the Bray-Curtis dissimilarity index. Bacteroides species (*B. uniformis, B. vulgatus,* and *B. dorei*), two Bifidobacterium species (*B. adolescentis* and *B. longum*), and *E. coli* were present with 5 % relative abundance greater than or equal to 5 % in mothers with B. *uniformis* being the most prevalent.

Table above displays a summary of all included studies assessing microbial composition of healthy birthers of term infants. Columns display study information regarding time points assessed, microbial taxa level(s) assessed and type of diversity (if composition and/or diversity analysis was performed), DNA sequencing method, and major findings. P-values showed for statistically significant findings, other values inputted as mean +/− standard deviation, ~ shows approximated values.

*Not all taxa levels mentioned analyzed relative abundance and therefore were not discussed in the review.

Note: for studies on beta diversity using clustering analysis

†indicates use of an unsupervised approach and

ǂindicates use of a supervised approach.

d, day(s), hr, hour(s), IndVal, indicator value, mo, month(s), OTU, operational taxonomic unit, PP, postpartum, wk, week(s).

Table 4

Factors Influencing and Conditions/Measures Associated with the Postpartum Gut Microbiome.

2a. Influencing Biological/ Environmental Factors

First author	Factors(s)	Analysis	Comp	Diversity	Major Findings
Abrahamsson et al. [17]	probiotic supp BF	culture: L. *reuteri* & *Lactobacillus*	genus, species	–	Oral supplementation with L. *reuteri* during the last month of pregnancy leads to increased L. *reuteri* in maternal stool samples at 1 wk PP when compared to placebo (P=.04).
Butts et al. [30]	mode of delivery BF	16S rRNA (V3-V4)	phylum, genus	–	No significant difference in bacteria abundances in PP maternal feces compared by ethnicity and delivery mode at phylum or genus level.
Carrothers et al. [23]	mode of delivery BF	16S rRNA (V1-V3)	phylum, genus	alpha & beta †	In 20 fully BF (≥4 months) women, at the phylum level, members of Firmicutes and Bacteroidetes were most abundant, followed by lesser amounts of Proteobacteria,
	dietary intake		phylum, genus	alpha & beta †	Verrucomicrobia, unclassified bacteria, and Actinobacteria. At the genus level, unclassified bacteria dominated followed by *Bacteroides, Faecalibacterium, Lachnospiracea incertae sedis* (denoted as *Lachnospiracea* unclassified in some figures), and *Prevotella*. There were no significant differences in relative abundance and alpha or beta diversity indexes by mode of delivery. No association was found between increased saturated fat consumption and enrichment of *Bacteroides* and *Parabacteroides*. Spearman rank correlations suggested that increased intake of pantothenic acid, riboflavin, vitamin B-6, and vitamin B-12 were related to increased relative abundance of *Prevotella* (r = 0.45, 0.39, 0.34, and 0.24, respectively; $P \leq 0.01$) and decreased relative abundance of *Bacteroides* (r = 20.55, 20.46, 20.32, and 20.35, respectively; $P \leq 0.01$). Intakes of copper, magnesium, manganese, and molybdenum were positively associated with Firmicutes (r = 0.33, 0.38, 0.44, and 0.51, respectively; $P \leq 0.01$) and negatively associated with Bacteroidetes (r = 20.38, 20.44, 20.48, and 20.53, respectively; $P \leq 0.01$). Increased protein intake was associated with decreased abundance of *Spirochaetes* ($P \leq 0.01$). Vitamin D intake was positively associated with *Dialister* abundance. Compared with all other quartiles, relative abundance of Proteobacteria was higher in individuals consuming the highest quartile of vitamin B-12 (P<.05). Evenness was higher in women grouped in the third quartile of vitamin B-12 intake (P<.05) compared with all other nutrient intake quartiles.
Cortes-martin et al. [37]	BF	16S rDNA metagenomic sequencing	phylum, family, genus	alpha & beta †	In BF women, there was significant changes in alpha diversity comparing four assessed longitudinal timepoints in PP using Chao1 index (P=.004). Chao1 microbial richness was decreased at 6 and 12 months compared to 3 weeks and 4 months (P<.05) However no significant changes were observed using Shannon's index. Increased abundances of Actinobacteria, Proteobacteria, Verrucomicrobia, *Bifidobacteriaceae, Coriobacteriaceae,* and *Akkermansia* observed in early lactation. 4 and 6 mo PP were similar in microbial composition, but different compared to early lactation period. Significant differences in beta diversity were seen between early and established/after-lactation timepoints.
Dahl et al. [27]	preterm vs term delivery mode of delivery	16S rRNA (V4)	phylum, family, genus	alpha & beta †	Firmicutes was the predominant phylum in both spontaneous preterm and term deliveries. Higher abundance of Firmicutes (P=.04) and lower abundance of Actinobacteria phylum (P=.01) was observed in preterm deliveries. Mothers who delivered preterm had lower OTUs abundance belonging to *Bifidobacterium* and *Streptococcus* genera and Clostridiales order. There is an association between low bacterial diversity and increased preterm delivery risk. One interquartile range (IQR) increase in alpha diversity was associated with 48 % (95 %CI: 4.2 %,72 %) lower odds of preterm birth and the association was stronger after controlling confounders including age, antibiotic use during pregnancy, ethnicity, body mass index, smoking, and education. PCoA showed no difference in the maternal beta diversity of preterm vs full-term deliveries. All participants were vaginal deliveries.
Dotterud et al. [21]	probiotic supp BF	qPCR	species	–	Prevalence and relative abundance of L. *acidophilus* La-5 (P<.005), L. *rhamnosus* GG (P<.005), and B. *animalis* (P < 0.005) were increased in mothers in probiotic group compared to placebo. Perinatal administration of the probiotic bacteria LGG, Bb-12, and La-5 leads to a significantly

					increased relative abundance of these bacteria in mothers 3 mo PP; no differences between groups in non-administered bacteria.
Enomoto et al. [22]	probiotic supp	16S rRNA (V6-V8), emulsion PCR, pyrosequencing	phylum	–	After administration of *Bifidobacterium* strains, B. *breve* and B. *longum* during the last month of pregnancy in the probiotic group, the proportion of Proteobacteria was significantly lower compared to placebo at 4–18 mos PP (P =.007). The proportion of Proteobacteria decreased in the probiotic group but increased in the control group of mothers at PP when compared with their proportions before beginning the study. Significantly increased proportions of Actinobacteria in the microbiota of mothers at PP compared to pregnancy.
Gronlund et al. [15]	probiotic supp BF	qPCR	genus, species	bifidobacterium diversity	Supplementation for 2 mos before until 2 mos after delivery with a probiotic containing L. *rhamnosus* and B. *longum* or with a probiotic containing L. *paracasei* and B. *longum* showed no significant differences in bifidobacterial diversity indexes between intervention groups. Neither probiotic intervention had effect on the colonization rates or bacterial counts of the genus *Bifidobacterium,* certain species of *Bifidobacterium* and *Clostridium,* and the species A. *muciniphila*, and S. *aureus*.
Halkjaer et al. [16]	probiotic supp	SSU rRNA	genus, species	alpha & beta †	Multi-strain probiotic containing *Bifidobacterium*, *Lactobacillus,* and *Streptococcus* administered at 14–20 gest wks until delivery can increase alpha diversity in obese women with an increase in *lactobacilli*, *bifidobacterial,* and S. *salivarus* over time until 2–3 ds postdelivery. Bray–Curtis dissimilarity between baseline samples and samples from gestational wk 27–30 and 36–37, and after birth were greater in probiotic vs placebo group (P = 3.72e – 6, 1.26e – 4, and 0.0014, respectively).
Hesla et al. [28]	other factors BF	16S rRNA (V3-V4), pyrosequencing	phylum, family, genus, species	alpha & beta	No significant influence of anthroposophic lifestyle on overall gut microbiota pattern.
Jost et al.[24]	mode of delivery BF	16S rRNA gene (V5-V6), qPCR, pyrosequencing	phylum, family, genus	alpha	Delivery and lactation do not induce significant alteration to the gut microbiota.
Mandal et al. [33]	dietary intake	16S rRNA (V4)	phylum, genus	alpha & beta †	Increased saturated fat intake was associated with decreased relative abundance of Firmicutes and Proteobacteria. Increased protein intake was associated with increased abundance of *Methanobrevibacter*. Vitamin D showed strongest statistical associations for both whole tree phylogenetic and Shannon's diversity. Significant inverse associations were observed for vitamin D, retinol and cholesterol (% change in whole tree phylogenetic diversity per unit increase of the vitamin; −7.8 %, P =.001, −5.6 %, P =.031, −5.3 %, P =.043, respectively). Only vitamin D was significantly inversely associated with Shannon's diversity (−5.1 % change in diversity per unit increase in vitamin D intake, P <.001). Beta diversity was not associated with dietary components. Vitamin D was associated with increases in Actinobacteria, Proteobacteria, Actinobacteria/Bacteriodetes, Proteobacteria/Firmicutes, and Other/Bacteroidetes. Vitamin E was associated with decreases in Proteobacteria relative to Actinobacteria, Firmicutes and other and increases in Other/Bacteroidetes. Retinol was associated with increases in Actinobacteria and Firmicutes.
Morais et al. [40]	preterm	qPCR	phylum, genus	–	Firmicutes was the most abundant phylum and *Bifidobacterium* was the most abundant genus in the samples from mothers of preterm and extremely preterm neonates. Lower abundance of *Lactobacillus* was found relative to other sub-dominant genera.
Paganini et al. [18]	other factors BF	16S rDNA (V3-V4), qPCR	phylum, genus, species	alpha	At baseline, among secretor mothers and among non-secretor mothers, the microbiota was composed of the phylum Actinobacteria (9.0 % and 8.7 % of the 16S rDNA reads), Firmicutes (73.3 % and 74.6 %), Bacteroidetes (12.5 % and 12.8 %) and Proteobacteria (4.1 % and 2.5 %). *Clostridium perfringens* was higher in abundance in non-secretor mothers compared to secretor mothers (P =.028). No other significant differences in gut microbiota composition and no differences phylogenetic diversity whole tree (alpha diversity) were observed between secretor mothers and non-secretor mothers.
Ribado et al. [19]	environmental	16S rRNA (V4), whole shotgun metagenomic sequencing	phylum, species	alpha, beta †	After introduction of triclosan-containing toothpaste, antibiotic-resistant species from Proteobacteria were enriched in stool samples of mothers. The most enriched organism in the exposed group was triclosan-resistant E. *coli*. TC exposure from wash products did not have effect on maternal gut microbiota. Diversity was not significantly decreased by exposure to TC-containing products at 2 (P

					=.729), 6 (*P* =.280), and 10 months (*P* =.201), however trended to a decrease in stool diversity at the 10-month visit.
Schei et al. [20]	probiotic supp BF	18S rRNA gene lTS1 region, qPCR	species	–	In mothers who consumed probiotic milk containing L. *acidophilus*, L. *rhamnosus*, and B. *animalis* subsp *lactis* from 36 gest wks to 3 mos PP, there was a significant increase in total fungal abundance (quantified by the amount of fungal DNA copies) compared to placebo at 3 mos PP (*P* =.01). S. *cerevisiae* (OUT 159) was underrepresented in the probiotic group, but with no statistical significance compared to mothers not administered probiotics in pregnancy (*P* =.07).
Turroni et al. [25]	mode of delivery BF	16S rRNA pyrosequencing (V6-V8), emulsion PCR	phylum, family, genus, species	–	All maternal samples from vaginal deliveries showed on average highest percent composition of Firmicutes, with Actinobacteria as sub-dominant. On the family level, *Clostridiales, Misc* was found to be predominant with *Bifidobacteriaceae* and *Lactobacillus, Misc* as sub-dominant. When looking at the Bifidobacterium genus specifically, *B. longum* was found with the highest prevalence with *B. adolescentis*, *B. bifidum* and *B. animalis* subsp. *lactis* in sub-dominant levels in that order on average.
Williams et al. [35]	BF	16S rRNA (V1-V3), PCR	phylum, genus,	alpha & beta †	Most abundant genus in maternal feces was *Bacteroides* (22.9 +/− 1.3 %). Maternal feces had greater richness (*P* <.0001) than infant feces and oral samples. Shannon diversity of maternal feces greater (*P* <.008) than other samples. No changes across time for alpha diversity of maternal fecal samples.
Yassour et al. [39]	BF	whole-genome shotgun metagenomic sequencing, qPCR	phylum, species	alpha & beta	Study population included mothers who breastfed. At the phylum level, mothers had high relative abundance of of Bacteroidetes and Firmicutes. Maternal samples contained 20 or more species above 1 % relative abundance. There were no differences in alpha diversity from pregnancy to postpartum. The maternal microbial communities displayed stability with significant overlap in the species-level composition measured by Bray-Curtis dissimilarity between timepoints from pregnancy to 3 mos PP relative to random subject pairings (*P* = 2.82e-11, 6.34e-08, calculated with *t*-test).

2b. Associated Health Conditions/Clinical Intermediate Measures

First author	Health Conditionand/or Clinical Measure	Method(s)	Comp	Diversity	Major Findings
Butts et al. [30]	BMI	16S rRNA (V3-V4)	phylum, genus	–	No significant differences in bacterial phylum or genus level composition were observed in mother's fecal microbiota based on BMI categories (normal, overweight and obese) at 6–8 wks PP.
Carrothers et al. [23]	BMI	16S rRNA (V1-V3)	phylum, genus	alpha & beta †	Spearman rank correlations showed increased current BMI (measured at each PP sampling period) of healthy lactating mothers was associated with increased relative abundance of *Parabacteroides* (r = 0.19; P ≤ 0.01) in fecal samples collected 1–3 mos PP. Results from univariate ANOVA for the effects of selected anthropometric variables on the relative abundance of individual bacterial groups and diversity indexes showed prepregnancy BMI was related to relative abundance of Firmicutes (46.5 % and 56.7 % in normal and overweight/obese women, respectively (P <.05). There were no significant differences in diversity indexes (PCA, NMDS) by current or prepregnancy BMI.
Cortés-Martín et al. [37]	UMs, BMI, weight, waist circumference, hip circumference & waist-to-hip ratio	16S rDNA metagenomic sequencing	phylum, genus, family, species	alpha & beta †	Urolithin metabotypes are based on the final urolithins produced from metabolism of dietary polyphenols ellagitannins by the gut-microbiota. Metabotype A only produces urolithin A and metabotype B produces urolithin A, urolithin B, and isourolithin A. Only the UM-A group showed changes in BMI and waist throughout the 3 PP stages. UM-A group only showed mean normoweight BMI values. Waist-to-hip ratio (WHR) reduction was only significant in UM-A group. Both groups (by delivery type) showed significant gradual reductions in BMI and waist (P <.05) from 3 wks to 4 mos PP. Hip and WHR reductions were only significant in the cesarean delivery group (P <.05). Anthropometric values including waist, BMI, WHR, and weight were associated with decreased *Clostridiaceae* family and its genera *Clostridium sensu stricto* and *Anaerobacter* which were decreased only in the UM-A group. Decreased levels of *Methanobrevibacter* and *Olsenella* (observed in UM-A group) were associated with reduced waist measurement during PP. In contrast, the increase of *Eggerthella, Gordonibacter, Erysipelotrichaceae incertae sedis,* and *Blautia,* which were significantly augmented in UM-A versus UM-B, was associated with the decrease of the mother's waist. UM-B (metabotype B) showed higher PP energy metabolism and was positively associated with microbial

					groups Archaea, *Methanobrevibacter*, *Ellagibacter* and *Prevotella*. Results showed distinct profiles between which urolithin metabotype was present. Determination of UMs in pregnant and lactating women may estimate predisposition to recovery of gut microbiota. The UM-A group modified their microbiota during PP, differing more and more from those of UM-B, while those of the UM-B had barely modified microbiota.
	Crusell et al. [26]	GDM	16 S rRNA (V1-V2)	genus & species	alpha & beta$^{\neq}$	Actinobacteria phylum and *Collinsella* genus were enriched at 8 mos PP in GDM group compared to healthy controls by linear discriminant analysis (LDA) using LEfSe (Linear discriminant analysis Effect Size). Actinobacteria and *Collinsella* were identified as taxonomic biomarkers of GDM. *Bacteroides* OTU_4999, *Isobaculum* OTU_595 and *Clostridium IV* OTU_109 were depleted and *Faecalibacterium* OTU_2674 was enriched both in the third trimester of pregnancy and 8 mos PP in GDM group compared to healthy controls. Also, *Eggerthella* OTU_184, *Faecalibacterium* OTU_3232, and *Lachnospiracea_incertae_sedis* OTU_2019 were depleted and *Faecalibacterium* OTU_3440, *Phreatobacter* OTU_107, *Alistipes* OTU_98, *Anaerovorax* OTU_538, *Collinsella* OTU_3860, and *Clostridium sensu stricto* OTU_77 were enriched at 8 mos PP in GDM group. No significant differences in alpha diversity (observed OTUs, Shannon's diversity and Pielou's evenness) or beta diversity were found in GDM vs non-GDM group. OTU richness was higher during late pregnancy compared with PP in both GDM and non-GDM groups.
	Lv et al. [32]	PE	16S rRNA (V4)	genus & species	alpha & beta $^{\neq}$	At the genus level, *Actinomyces* was enriched at 1 wk PP and *Clostridium* was enriched at 6 wks PP in PE mothers compared to normotensive, uncomplicated controls. *Porphyromonas gingivalis* and unclassified species of *Pediococcus* and *Dehalobacterium* were depleted at 1 wk PP in PE mothers. An unclassified species of *Streptococcus* was enriched in PE mothers at 6 wks. Alpha and beta diversity were not significantly different between PE and non-PE groups. Alpha and beta diversity also did not change significantly from antepartum to 1 wk or 6 wks PP in PE and non-PE participants.
	Stanislawski et al. [29]	(OW/OB & GWG	16S rRNA (V4)	order, family, genus, species	alpha	*Blautia* sp. OTU (P =.007), WAL_1855D sp. OTU (P =.007), *Blautia* (P =.019), and WAL_1855D (P =.004) were increased in mothers with excessive GWG compared to mothers in the non-GWG group. Clostridiales OTU (P =.003) and *Lachnospiraceae* OTU (P =.022) were increased in maternal OW/OB. *Lachnospira* (P =.001), unclassified *Christensenellaceae* (P =.003), *Finegoldia* (P =.004), *Parabacteroides* (P =.167), *Clostridiaceae* OTU (P =.007), *Parabacteroides* sp. OTU (P =.009), *Finegoldia* sp. OTU (P =.005), and *Bifidobacterium* sp. OTU (P =.023) were decreased in maternal OW/OB. Alpha diversity (Shannon diversity and PD whole tree) were significantly lower among OW/OB women after controlling for maternal age, education, Norwegian ethnicity, parity, twins, and smoking during pregnancy. In women with a full term pregnancy, excessive GWG was not associated with significant differences in alpha diversity (Shannon: $\beta = -0.1$, 95 % CI − 0.3, 0.1; P =.53; PD: $\beta = -0.1$, 95 % CI − 1.9, 1.8; P =.96; observed species: $\beta = -4.0$, 95 % CI − 28.3, 20.2; P =.75).
	Van der Giessen et al. [34]	IBD, (UC, CD)	16S rRNA (V4)	genus & species	alpha & beta $^{\neq}$	R. *bromii* was increased in CD patients compared to UC patients. *Bacteroides ovatus*, *Streptococcus,* and an unclassified member of *Lachnospiraceae* (higher in 3rd trimester as well) was increased in UC patients compared to CD patients. Beta diversity did not differ significantly in IBD patients over time (prepregnancy to PP). Regarding alpha diversity, richness (Faith's phylogenetic diversity) and evenness (Pielou) were not significantly different from prepregnancy to the postpartum. When comparing UC and CD at a given time point, significant differences in beta diversity were observed in the prepregnancy samples (P =.041) in unweighted and weighted UniFrac, but not first, second, or third trimester or PP.
	Zhou et al. [36]	BMI	16S rRNA (V4)	genus & species	alpha & beta $^{\neq}$	BMI was positively correlated with *Allisonella* and negatively correlated with *Holdemania, Coprobacillus,* and *Ruminococcaceae*. UCG.014
		PPD				In both groups, the proportion of Firmicutes was the highest among all phyla, which was higher in the HC group (88.91 %) than that in PPD group (74.57 %). *Faecalibacterium* (P =.003), *Phascolarctobacterium* (P =.022), *Butyricicoccus* (P =.024), and *Megasphaera* (P =.047) were decreased in the PPD group compared to the HC group. Using LEfSe analysis (P <.05, LDA value > 2), *Enterococcus* and *Escherichia_Shigella* were enriched in the PPD group and *Faecalibacterium, Phascolarctobacterium, Butyricicoccus, Lachnospiraceae, Acidaminococcaceae, Eubacterium_xylanophilum,* and *Megasphaera* were depleted in the PPD group. Edinburgh Postnatal Depression Scale (EPDS) scores were positively correlated with *Dialister, Clostridium.sensu.stricto.1, Senegalimassilia,* and *Lachnospiraceae.FCS020.group* and negatively

			correlated with *Lachnospiraceae.UCG.004, Phascolarctobacterium, Lachnospiraceae.UCG.001, Lachnospiraceae.UCG.006,* and *Lachnospiraceae.ND3007.group*. 17-item Hamilton depression rating scale (17-HAMD) scores were positively correlated with *Escherichia.Shigella*, *Dialister,* and *Enterococcus* and negatively correlated with *Butyricicoccus, Lachnospiraceae.UCG.001, Lachnospiraceae.ND3007.group, Faecalibacterium, Tyzzerella.3,* and *Megasphaera*. There were no significant differences in alpha diversity including observed species, evenness, Shannon, and Faith-PD indices (P =.669, 0.526, 0.367, and 0.435, respectively) between the PPD group and HC group. Sample-based differences in the PPD group were significantly higher than the HC group (Wilcoxon rank-sum test: P = 2e-14). With PCoA, there was a significant difference in bacterial communities between the PPD group and HC group (P =.038). These β-diversity indices in the HC group were more centralized than those in the PPD group.

Table above displays summary of studies that 2a) assessed biological/environmental factors or 2b) health conditions or clinical measures that are influencing show associated microbial changes in all mothers. r values display Spearman rank's correlation, P-values display results with statistical significance.

Note: for studies on beta diversity using clustering analysis

†indicates use of an unsupervised approach and

‡indicates use of a supervised approach.

CD, Crohn's disease, DNA, deoxyribonucleic acid, Early-PE, early onset pre-eclampsia, GDM, gestational diabetes mellitus, GWG, gestational weight gain, HC, healthy control, IBD, inflammatory bowel disease, IndVal, indicator value, OTU, operational taxonomic unit, OW/OB, overweight/obese, PCR, polymerase chain reaction, PP, postpartum, PPD, postpartum depressive disorder, qPCR, real-time polymerase chain reaction, rRNA, ribosomal ribonucleic acid, UC, ulcerative colitis, UM, urolithin metabotype.