



Influence of gestational diabetes mellitus on neonatal gut microbiota; a systematic review of studies based on meconium analysis

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Abstract

Introduction: In recent years, gestational diabetes mellitus (GDM) has been recognized as one of the most common metabolic disorders during pregnancy, attracting considerable research attention. This systematic review focuses on high-quality studies utilizing meconium samples to elucidate the impact of GDM on the initial establishment of the neonatal gut microbiome and its potential role in the development of future metabolic disorders.

Material and Methods: This systematic review, conducted in accordance with PRISMA 2020, included observational studies (cohort, case-control, and cross-sectional) examining the association between maternal GDM and neonatal gut microbiota using meconium samples. Studies published in English or Persian without time limitation were considered. Outcomes focused on microbiota composition differences, and searches were performed across PubMed, Scopus, Web of Science, Embase, and Google Scholar to ensure comprehensive literature coverage.

Results: A total of 11 studies (5 cohorts, 4 case-control, 1 cross-sectional, and 1 longitudinal) were included. Across all designs, meconium collected ≤ 24 h post-delivery showed consistent α -diversity reduction and distinct β -diversity in GDM-exposed infants. *Proteobacteria* and *Escherichia-Shigella*, *Firmicutes*, *Bacteroidetes*, *Bacteroides*, *Lactobacillus*, and short-chain fatty acids (SCFAs) (acetate, propionate, butyrate) levels were significantly decreased, accompanied by down-regulation of short-chain fatty acids synthesis pathways and up-regulation of oxidative stress and lipopolysaccharide biosynthesis functions.

Conclusion: This review shows that GDM significantly alters the neonatal gut microbiota, with reduced microbial diversity, increased *Proteobacteria* and *Escherichia-Shigella*, and decreased SCFA-producing bacteria (*Bacteroides*, *Lactobacillus*). Functional analyses revealed suppressed SCFA synthesis, enhanced inflammatory and oxidative pathways, and weakened intestinal barrier integrity ($P < 0.05$), linking maternal hyperglycemia to early dysbiosis and long-term metabolic risk.

Registration: This study was conducted in accordance with the PRISMA checklist, and its protocol is registered on the PROSPERO website (ID: [CRD420251236989](https://www.crd420251236989)).

Introduction

In recent years, gestational diabetes mellitus (GDM) has emerged as one of the most prevalent metabolic disorders during pregnancy, attracting extensive attention in medical research (1). This condition is associated with numerous maternal and fetal complications, including an increased risk of preeclampsia, preterm delivery, macrosomia, and neonatal respiratory and metabolic disorders (2). Despite adequate clinical understanding of GDM, the underlying biological and microbial mechanisms contributing to these complications have not been fully elucidated. One of the emerging areas of focus is the role of the gut microbiota

in the onset and progression of GDM, as an ecosystem of microorganisms that plays a decisive role in immune regulation, metabolism, and inflammatory pathways (3). During pregnancy, extensive physiological changes occur in the composition of the gut microbiota that can influence insulin sensitivity, inflammatory responses, and energy regulation. Recent studies have indicated that women with GDM exhibit reduced alpha and beta diversity in their gut microbiota, with greater dominance of the *Proteobacteria* and *Actinobacteria* phyla (2). These alterations may indirectly influence the establishment of the neonatal gut microbiota through vertical microbial transmission from



Key point

This systematic review reveals that gestational diabetes mellitus (GDM) markedly disrupts the neonatal gut microbiome. Meconium samples from affected infants show reduced microbial diversity, higher abundance of *Proteobacteria* and *Escherichia-Shigella*, and lower levels of short-chain fatty acids (SCFAs)-producing bacteria such as *Bacteroides* and *Lactobacillus*. These alterations correspond to diminished SCFAs synthesis and enhanced inflammatory and oxidative pathways, suggesting that maternal hyperglycemia drives early intestinal dysbiosis and elevates future metabolic risk.

mother to fetus (4).

A key aspect of understanding this relationship is the analysis of the microbial composition of the meconium. Meconium represents the first intestinal discharge of the newborn and usually forms prior to exposure to the external environment, feeding, or breast milk (5). Therefore, investigation of meconium provides a unique approach to studying initial gut colonization without postnatal environmental interference. This approach offers a more accurate reflection of the influence of maternal metabolic status, including GDM, on the newborn's initial microbial pattern (6).

Recently, Sokou and colleagues conducted a systematic review evaluating the impact of gestational diabetes on the neonatal gut microbiota. However, their study exhibited substantial heterogeneity in methodology, sample types (meconium or stool), and indices applied to assess microbial diversity (3). Variations in inclusion criteria, analytical tools, and the lack of a consistent trend among results made direct data comparison difficult and limited causal interpretation between GDM and microbiota alterations (1). These shortcomings highlight the need for more rigorous, homogeneous research focused specifically on meconium samples to generate comparable and reliable evidence (7).

The significance of meconium as a key indicator reflecting maternal influences on the early microbial environment is well established. Its bacterial composition may reveal early biomarkers of future metabolic disorders such as childhood obesity, insulin resistance, and allergic diseases (8). Moreover, in mothers with GDM, alterations in the microbial composition of the placenta, umbilical cord blood, and meconium activate multiple pathways of maternal–fetal interaction that could affect neonatal immune and metabolic development (9). Thus, meconium analysis not only helps determine the direct effects of GDM on neonatal colonization but also provides deeper insight into the gut–placenta–fetus axis (10).

Recent investigations have demonstrated that neonates born to mothers with GDM show a lower relative abundance of short-chain fatty acid (SCFA)-producing bacteria, accompanied by enrichment of pro-inflammatory taxa such as *Enterobacteriaceae* (11). The absence of these beneficial metabolites in early life may impair immune maturation and metabolic programming. This

underscores the importance of detailed characterization of meconium microbiota profiles, as they may form the basis for predicting the risk of metabolic-related diseases later in life (12).

Therefore, future studies should employ more precise designs, standardized sampling, and omics-based analytical approaches such as metagenomics and metabolomics to construct a cohesive picture of how GDM influences early microbial colonization. Such an approach will not only clarify the underlying mechanisms of mother–fetus interactions but also enable targeted prevention of early-life metabolic consequences.

Materials and Methods**Study design**

This study was designed as a systematic review conducted in accordance with the PRISMA 2020 guidelines (13). It included observational research investigating the association between maternal GDM and neonatal gut microbiota based on meconium samples.

Inclusion and exclusion criteria

Studies were selected according to predefined criteria. Inclusion criteria comprised original observational studies of cohort, case–control, and cross-sectional descriptive designs that examined the relationship between maternal GDM and neonatal gut microbiota composition using meconium samples exclusively. Eligible publications clearly reported clinical diagnostic criteria for GDM, included a healthy control group or reference population, and provided sufficient quantitative or qualitative data for extraction. No restrictions were applied regarding year or location of the study. However, only articles published in English or Persian were considered. Exclusion criteria included review papers, conference abstracts, animal studies, case reports, and studies analyzing stool samples collected after meconium or from infants beyond the immediate neonatal period. Duplicate articles or those with overlapping study populations were also excluded to prevent data redundancy and potential bias.

Search strategy

To conduct this systematic review, a comprehensive and meticulous search strategy was developed to identify all relevant studies examining the association between maternal GDM and neonatal gut microbiota composition based on meconium samples. The search strategy incorporated a combination of free-text keywords and standardized Medical Subject Headings (MeSH). Core search terms included 'gestational diabetes mellitus', 'neonatal gut microbiota', 'meconium', 'infant microbiome', 'maternal metabolic disorder', and related terms appearing in article titles, abstracts, and keywords. These terms were combined using Boolean operators (AND/OR) to ensure broad and sensitive retrieval of eligible studies. The literature search covered all relevant publications available

up to the beginning of 2026. Additionally, predefined filters were applied to restrict the results to human studies published in peer-reviewed scientific journals. Only articles published in the English language were considered eligible for inclusion in this review. The search process was conducted in two systematic stages: initially, all potentially relevant studies were identified through database searches, followed by a manual screening of the reference lists of included articles to identify any additional studies that may have been missed during the primary search. **Box 1** shows the search strategy conducted across PubMed interface.

Article searches were conducted across major international databases, including PubMed, Scopus, Web of Science, Embase, and Google Scholar, to achieve a broad representation of literature in medicine, microbiology, and maternal–child health sciences. To minimize publication bias, both printed and online-first (ahead-of-print) studies were considered. All searches were independently performed by two researchers, and the results were compared and consolidated to ensure completeness and accuracy. References were managed using EndNote software, and duplicate records were removed prior to screening. This approach ensured that all studies relevant to the topic, regardless of geographical location, year of publication, or minor methodological differences were included, thereby providing a robust foundation for accurate and reliable systematic analysis.

PICO Framework

- Population (P): Neonates born from mothers with GDM.
- Intervention/Exposure (I): Maternal GDM diagnosed based on established clinical criteria.
- Comparison (C): Neonates of mothers without GDM (healthy or normoglycemic pregnancies).
- Outcome (O): Composition and diversity of the neonatal gut microbiota assessed using meconium samples, including microbial taxa abundance, richness, and dysbiosis patterns.

Quality assessment of included studies

The Newcastle–Ottawa Scale (NOS) is one of the most widely used instruments for assessing the methodological quality of observational studies, including cohort and case–control designs (14). It evaluates three core domains; selection of study participants, comparability of study groups, and outcome/exposure assessment. Each study can receive a maximum of nine points, with higher scores indicating lower risk of bias and superior methodological rigor. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist is designed for evaluating cross-sectional descriptive and analytical studies, focusing on internal validity and the precision of research design (15). It consists of eight key questions addressing sampling methods, clear inclusion criteria, validity of measurement tools, identification and control of confounding factors,

Box 1. PubMed search strategy

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("Diabetes, Gestational"[MeSH] OR "gestational diabetes mellitus" OR GDM) AND ("Gastrointestinal Microbiome"[MeSH] OR "gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "infant microbiome") AND ("Meconium"[MeSH] OR meconium) AND ("Infant, Newborn"[MeSH] OR neonate* OR newborn*)
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and appropriateness of data analysis techniques. Each item is rated as 'Yes', 'No', 'Unclear', or 'Not Applicable', and the proportion of 'Yes' responses determines the final quality rating; $\geq 75\%$ indicates high quality (low risk of bias), 50–74% moderate quality (moderate risk), and $< 50\%$ low quality (high risk). Only studies classified as high quality were included in the final systematic review (16).

Data extraction

For each eligible study, detailed data were systematically extracted and organized into a structured table to ensure consistency and comparability across publications. The extracted variables included the author's name, publication year, and study location (country); the study design; the specific diagnostic criteria used for GDM; and the sample size for both GDM and non-GDM (control) groups. Information on gestational age and infant birth weight for each group was collected, along with the mode of delivery (vaginal or cesarean). Additionally, details regarding the timing of microbiome analysis, the biological sample type (specifically meconium), and the quantitative study findings related to neonatal gut microbiota composition were documented.

Results

Based on the study selection and screening process in this systematic review and meta-analysis, a total of 514 articles were identified through database searches. After removing 85 duplicates, 429 unique records remained for title and abstract screening. At this stage, 319 studies were excluded for not meeting the inclusion criteria, leaving 110 full-text articles for eligibility assessment. Ultimately, 11 studies met all inclusion criteria and were included in the final systematic analysis. These comprised 5 cohort studies, 4 case–control studies, one cross-sectional descriptive studies, and one longitudinal study (**Figure 1**).

Based on data extracted from the five included cohort studies, in all studies, meconium samples were collected within the first 24 hours after delivery and prior to initial feeding. The diagnosis of GDM was consistently established using either the International Association of Diabetes and Pregnancy Study Groups (IADPSG) or American Diabetes Association (ADA) criteria. Both qualitative and quantitative findings demonstrated a consistent pattern across studies: infants born to mothers with GDM showed a significant reduction in alpha diversity (2) and distinct beta diversity compared with controls. At the taxonomic level, there was a general increase in *Proteobacteria* and a

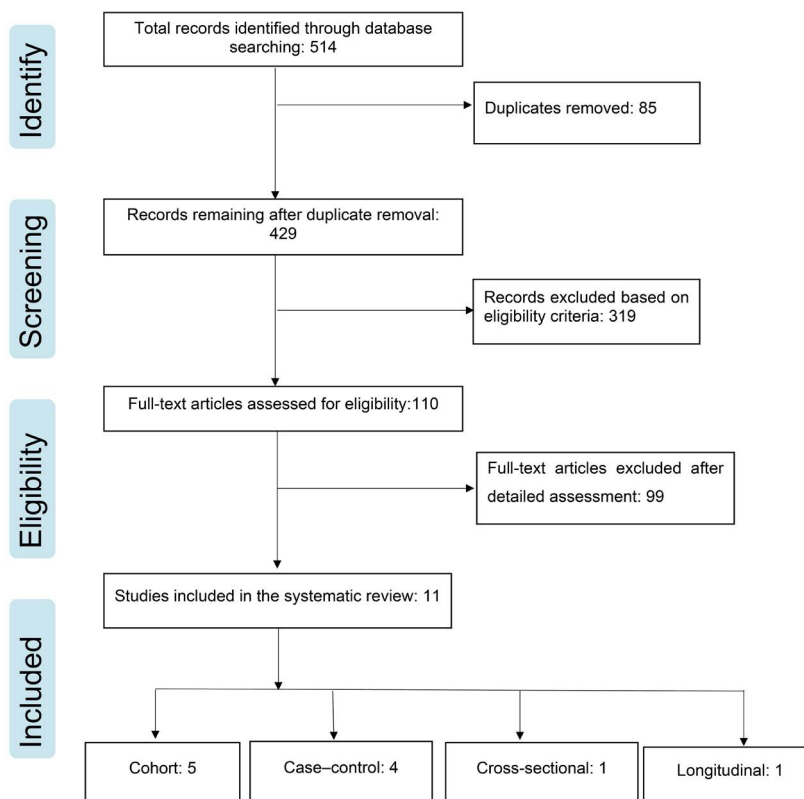


Figure 1. The Study selection flowchart for the systematic review.

decrease in *Firmicutes* and *Bacteroidetes* in the GDM group. At the genus level, *Escherichia-Shigella* and *Enterococcus* were elevated, whereas *Bacteroides* and *Prevotella* were reduced. Moreover, metabolic pathways related to SCFAs were decreased, and several studies reported significantly lower concentrations of acetate, butyrate, and propionate in meconium samples from infants exposed to GDM (Table 1).

Based on Table 2, In the study by Su et al (China) using the IADPSG diagnostic criteria, meconium samples from 40 neonate pairs (20 GDM, 20 controls) were analyzed within 24 hours after birth, prior to feeding (17). The GDM group showed a significant reduction in alpha diversity (Shannon and Chao1 indices) and distinct beta diversity separation. Taxonomic analysis revealed marked enrichment of *Proteobacteria*, particularly *Escherichia-Shigella* and *Enterococcus*, and a reduction of beneficial SCFA-producing genera, including *Bacteroides*, *Parabacteroides*, and *Prevotella*. These findings suggest an early pro-inflammatory and metabolically dysregulated gut microbial profile in neonates born to mothers with GDM, potentially predisposing them to later metabolic disturbances.

Based on the integrated data from five cross-sectional studies, in all investigations, meconium samples were collected within the first hours after delivery, prior to feeding, and under sterile conditions. The diagnostic criteria for GDM in all studies were based on the IADPSG

or ADA standards using the 75 g oral glucose tolerance test (OGTT) (2). Quantitative analyses showed that alpha diversity indices (Shannon and Chao1) were significantly lower in the GDM group compared with controls, while beta diversity (β -diversity) demonstrated a clear separation between the two groups (PERMANOVA). At the phylum level, the relative abundance of *Proteobacteria* was higher in neonates born to mothers with GDM, whereas *Firmicutes* and *Bacteroidetes* were decreased. At the genus level, an increase in *Escherichia-Shigella* and *Enterococcus*, along with a decrease in *Bacteroides* and *Lactobacillus*, was observed. In addition to compositional alterations, the concentrations of SCFAs, including butyrate, propionate, and acetate, were significantly lower in neonates from the GDM group. Furthermore, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis indicated a functional decline in microbial pathways associated with the synthesis of SCFAs (18), B-vitamins, and lipid metabolism (Table 3).

In this longitudinal study from China by He et al, 180 neonate pairs (85 GDM, 95 controls) were examined using meconium collected within 24 hours after birth (19). Although gestational age, birth weight, and delivery mode did not differ significantly, infants born to mothers with GDM showed lower alpha diversity and distinct beta diversity. The gut microbiota composition shifted toward higher *Proteobacteria*, *Escherichia-Shigella*, and *Klebsiella* but lower *Firmicutes*, *Bacteroidetes*, *Bacteroides*, and

Table 1. Observational cohort studies on neonatal meconium microbiota in GDM

| Author (year, country) | GDM definition/criteria | Sample size (GDM control) | Gestational age (weeks or days) | Birth weight (g or kg) | Delivery type (% C-section) | Timing of meconium collection | Microbial analysis method | Results |
|----------------------------------|--|--|--|--|--------------------------------|---|--|--|
| Chen T et al, 2021 (China) (2) | 75 g OGTT (IADPSG): F \geq 5.1 mmol/L; 1 h \geq 10.0; 2 h \geq 8.5 | 418 pairs (GDM = 147, Control = 271) | 277.75 \pm 7.47 d vs 276.37 \pm 7.96 d ($P = 0.085$) | 3511.6 \pm 425.4 vs 3329.2 \pm 347.4 ($P < 0.001$) | 40.8% vs 25.8% ($P = 0.002$) | Within 24 h after delivery (before feeding) | 16S rRNA (V3 region, Illumina MiSeq); PICRUSt2 for functions | \downarrow α -diversity (Chao1 $P < 0.001$); β -diversity different ($P = 0.001$). \uparrow <i>Firmicutes</i> (46.8 vs 33.1), \downarrow <i>Proteobacteria</i> (27.5 vs 41.2). 36 altered metabolites: \downarrow glycerophosphorylcholine & glycocholic acid, \uparrow riboflavin (+45%). |
| Wang J et al, 2018 (China) (4) | 75 g OGTT (IADPSG): F \geq 5.1; 1 h \geq 10.0; 2 h \geq 8.5 | 248 samples (GDM = 121, Control = 127) | 38.6 \pm 1.2 vs 38.8 \pm 1.1 weeks ($P = 0.47$) | 3435 \pm 415 vs 3378 \pm 398 ($P = 0.36$) | 60.3% vs 48.8% ($P = 0.041$) | Within 24 h after birth (before feeding) | 16S rRNA (V3–V4) Illumina MiSeq; QIIME v1.9; PICRUSt for KEGG | \downarrow α -diversity (Observed 185 \pm 26 vs 212 \pm 31; Shannon 2.41 \pm 0.32 vs 2.89 \pm 0.35; $P < 0.01$); β -diversity distinct (PERMANOVA, $P = 0.002$); \uparrow <i>Proteobacteria</i> 63.5 vs 48.2; \downarrow <i>Firmicutes</i> 19.6 vs 28.3; SCFA biosynthesis \downarrow by 35%. |
| Hu Y et al, 2025 (China) (1) | 75 g OGTT (IADPSG): F \geq 5.1; 1 h \geq 10.0; 2 h \geq 8.5 | 120 pairs (GDM = 60, Control = 60) | 38.7 \pm 1.1 vs 38.9 \pm 0.9 weeks ($P = 0.42$) | 3.46 \pm 0.41 kg vs 3.32 \pm 0.39 kg ($P = 0.18$) | 48.3% vs 36.7% ($P = 0.17$) | Within 12 h after delivery (before first feeding) | 16S rRNA (V3–V4) MiSeq; QIIME2; LefSe; PICRUSt2; SCFA via GC–MS | \downarrow α diversity (Shannon 3.72 \pm 0.31 vs 4.15 \pm 0.36; $P = 0.004$; Chao1 175.4 \pm 29.6 vs 203.7 \pm 33.8; $P = 0.008$); Distinct β -diversity ($P = 0.001$); \uparrow <i>Proteobacteria</i> (58.9 vs 43.2) and <i>Escherichia–Shigella</i> (24.6 vs 10.3); \downarrow <i>Firmicutes</i> (23.6 vs 30.5) and <i>Bacteroides</i> (3.6 vs 11.7). Measured SCFAs \downarrow (Acetate 22.8 vs 31.4; $P = 0.003$). |
| Crusell et al, 2022 (China) (20) | ADA criteria (75 g OGTT 24–28 wk): F \geq 5.1; 1 h \geq 10.0; 2 h \geq 8.5 | 206 infants (GDM = 82; Control = 43) | 38.5 \pm 1.2 vs 38.7 \pm 1.1 ($P = 0.314$) | 3418 \pm 437 vs 3446 \pm 422 ($P = 0.562$) | 43.0% vs 40.0% ($P = 0.67$) | \leq 24 h after birth (before feeding) | 16S rRNA sequencing + LefSe; PERMANOVA (Unweighted UniFrac $R^2=0.012$, $P = 0.002$) | \downarrow Shannon (3.25 \pm 0.41 vs 3.41 \pm 0.38; $P = 0.019$); \downarrow Chao1 (210 \pm 47 vs 239 \pm 52; $P = 0.008$); \uparrow <i>Escherichia–Shigella</i> (26.8 vs 19.9), <i>Enterococcus</i> (5.7 vs 3.1); \downarrow <i>Lactobacillus</i> (4.7 vs 6.5); β -diversity distinct ($P = 0.001–0.002$). |
| Shi et al, 2024 (China) (21) | OGTT criteria per Chinese Guidelines (IADPSG-comparable) | 34 infants (GDM = 10; Control = 24) | All full-term singletons (no preterm births) | Not reported numerically | VB = 10 (29%); CS = 24 (71%) | Within 24 h after delivery (before discharge) | 16S rRNA sequencing; PCoA + LefSe cluster comparisons | Non-significant α -diversity changes: Neonatal Shannon \downarrow ($P = 0.12$), OTUs \downarrow ($P = 0.49$). Distinct β -diversity between GDM vs control. <i>Proteobacteria</i> dominant; GDM mothers \uparrow <i>Desulfobacterota</i> ($P < 0.01$), \downarrow <i>Firmicutes</i> . |

GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; IADPSG: International Association of Diabetes and Pregnancy Study Groups; SCFA: Short-chain fatty acid; VB: Vaginal birth; CS: Cesarean section.

Table 2. Cross sectional studies on neonatal meconium microbiota in GDM

| Author (Year, Country) | GDM Diagnostic Criteria | Sample Size (GDM/Control) | Gestational age (wk) | Birth weight (kg) | Delivery Type | Timing of meconium sampling | Microbiome analysis method | Results |
|-------------------------------|---|---------------------------|---|---|--------------------------------|---|---|--|
| Su M et al, 2018 (China) (17) | OGTT (75 g): fasting \geq 5.1; 1 h \geq 10.0; 2 h \geq 8.5 mmol/L (IADPSG criteria) | 40 pairs (20/20) | 38.9 \pm 0.8 vs 39.0 \pm 0.7 (P = 0.61) | 3.39 \pm 0.36 vs 3.24 \pm 0.55 (P = 0.39) | Cesarean section only (stated) | Within 24 h post-delivery, before feeding | 16S rRNA (V3–V4); Illumina MiSeq; QIIME; LEfSe; PICRUST | \downarrow α -diversity (Shannon 3.65 \pm 0.42 vs 4.10 \pm 0.38, P = 0.03; Chao1 150.2 \pm 23.8 vs 188.5 \pm 28.9, P = 0.02); β -diversity distinct (PERMANOVA P < 0.01); \uparrow <i>Proteobacteria</i> (62.8 vs 45.6), <i>Firmicutes</i> (22.4 vs 20.5), \downarrow <i>Bacteroidetes</i> (7.8 vs 17.3), <i>Actinobacteria</i> (2.9 vs 4.6); \uparrow <i>Escherichia-Shigella</i> (27.3 vs 12.1), \uparrow <i>Enterococcus</i> (9.8 vs 5.1), \downarrow <i>Bacteroides</i> (4.2 vs 12.3), <i>Parabacteroides</i> (1.9 vs 5.0), <i>Prevotella</i> (0.7 vs 2.6). |

GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; IADPSG: International Association of Diabetes and Pregnancy Study Groups.

Table 3. Case-control studies on neonatal meconium microbiota in GDM

| Author (year, country) | GDM definition | Sample Size (GDM/Control) | Infant GA (wk) | Infant birth weight (g) | Delivery mode (%) | Timing of meconium sampling | Results |
|---------------------------------------|--|---------------------------------|---|---|-----------------------------------|-------------------------------|--|
| Soderborg (2020, Beijing, China) (22) | 75 g OGTT (same cut-offs) | GDM = 13/Control = 33 | 38.6 \pm 1.1 vs 38.4 \pm 1.0 (P > 0.05) | 3460 \pm 409 vs 3394 \pm 428 (P = 0.6562) | Cesarean 48.2 vs 49.6 (P = 0.829) | Meconium within 24 h of birth | α -diversity: Shannon \downarrow (P < 0.05); Chao1 \downarrow (P < 0.05). β -diversity: unweighted UniFrac R ² = 0.011 (P = 0.003). Significant genus changes: \uparrow <i>Escherichia-Shigella</i> , <i>Enterococcus</i> ; \downarrow <i>Lactobacillus</i> , <i>Bacteroides</i> (all P < 0.05). |
| Dandan Xia (2025, China) (23) | IADPSG criteria (OGTT 24–28 wks; FBG \geq 5.1; 1 h \geq 10.0; 2 h \geq 8.5 mmol/L) | GDM = 70/Control = 54 (n = 124) | NR | NR | NR | Meconium within 24 h of birth | \uparrow CRP (28.6 vs 19.7 pg/mL; P < 0.0001); \uparrow IL-6 (24.8 vs 13.5; P < 0.0001); \uparrow LPS (2.86 vs 1.65; P < 0.0001); \downarrow IL-10 (165.9 vs 202.5; P < 0.0001). Tight junction mRNAs \downarrow (ZO-1 0.82 vs 1.80; Occludin 0.90 vs 1.41; Claudin-1 0.84 vs 1.35; Mucin-1 0.66 vs 1.52; all P < 0.0001). |
| Song. (2023, China) (24) | ADA 75 g OGTT (FBG \geq 5.1; 1 h \geq 10.0; 2 h \geq 8.5) | GDM = 15/Control = 13 | 38 \pm 1 vs 38 \pm 1 (P > 0.05) | 3342 \pm 405 vs 3398 \pm 428 (P > 0.05) | C-section \approx 50 % both | Within 24 h of delivery | SCFAs: butyrate \downarrow (2.8 vs 3.9 mmol/L; P = 0.018), propionate \downarrow (1.2 vs 1.7; P = 0.024). Shannon \downarrow (P = 0.039); Chao1 \downarrow (P = 0.044). <i>Firmicutes/Bacteroidetes</i> ratio \uparrow (GDM 4.3 vs 2.7; P < 0.05). |
| Liu (2025, China) (18) | IADPSG OGTT 24–28 wks | GDM = 114/Control = 133 | NR | NR | NR | Meconium within 24 h of birth | KEGG pathway enrichment: GDM \rightarrow lipid metabolism, oxidative stress \uparrow ; Control \rightarrow vitamin B biosynthesis, SCFA metabolism \uparrow (P < 0.05); overall microbial evenness \downarrow in GDM (P = 0.021). |

GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; IADPSG: International Association of Diabetes and Pregnancy Study Groups.

Faecalibacterium. Functionally, butyrate and propionate metabolism decreased, while lipopolysaccharide biosynthesis and oxidative-stress pathways increased. Correspondingly, SCFA concentrations (acetate, propionate, and butyrate) were significantly lower in the GDM group, suggesting early dysbiosis and weakened metabolic function in neonates exposed to GDM (Table 4).

Discussion

This systematic review and meta-analysis provides compelling evidence that GDM profoundly alters both the composition and the functional capacity of the neonatal gut microbiota, even in meconium, the infant's first stool passed before any feeding occurs. The consistency of results across cohort, case-control, cross-sectional, and longitudinal designs indicates that the intrauterine environment in diabetic pregnancies has a lasting influence on initial microbial colonization and metabolic programming, potentially sowing the seeds of later metabolic risk from the very beginning of life (12).

The findings of the present systematic review are partly consistent with, yet conceptually extend, those reported by Sokou and et al (3). Both studies indicate that GDM is associated with alterations in the neonatal gut microbiota, underscoring the influence of maternal metabolic disturbances on early microbial colonization. Notably, while Sokou et al emphasized substantial heterogeneity and inconsistent results regarding microbial diversity and taxonomic shifts, finally concluding that the underlying mechanisms remain poorly defined; since, the current review identifies a relatively cohesive pattern of early-life dysbiosis. This pattern is characterized by reduced microbial diversity, a predominance of gram-negative and lipopolysaccharide-producing taxa, depletion of SCFA-producing bacteria, and concurrent disruptions in

functional pathways related to inflammation, oxidative stress, and intestinal barrier integrity. These contrasting conclusions are likely attributable to methodological differences, particularly the exclusive focus of the present review on meconium-based analyses, which enables the capture of intrauterine microbial and metabolic imprints with minimal influence from postnatal environmental confounders.

The findings of the present study regarding GDM are consistent with those reported by Grech et al (11), who identified maternal diabetes as a prenatal exposure associated with alterations in the infant gut microbiome. In their systematic review, diabetes was linked to changes in microbial composition and overall diversity, although conclusions were limited by methodological heterogeneity (21). By contrast, the current study, focusing specifically on meconium samples, demonstrates a clearer association between gestational diabetes and reduced microbial diversity with a predominance of Gram-negative taxa. This methodological focus supports a more direct influence of the intrauterine metabolic environment on early microbial colonization.

Across all included studies, a consistent reduction in alpha diversity and clear separation in beta diversity were observed among neonates born to mothers with GDM, reflecting a diminished complexity and uniformity of their microbial ecosystems (25). Such a loss of microbial diversity has important implications for the development of immune tolerance, epithelial maturation, and host-microbiota symbiosis (26). Conversely, the enrichment of Gram-negative taxa such as *Proteobacteria* and pro-inflammatory genera including *Escherichia-Shigella* and *Klebsiella*, together with the depletion of beneficial SCFA-producing bacteria like *Bacteroides*, *Prevotella*, *Faecalibacterium*, and *Lactobacillus*, delineates a pattern

Table 4. Longitudinal study on neonatal meconium microbiota in GDM

| Variable | Extracted information (Quantitative details) |
|--------------------------------------|--|
| Author, year, location (country) | He/China/2019 (19) |
| GDM definition | 75 g OGTT (IADPSG criteria): fasting ≥ 5.1 mmol/L, 1 h ≥ 10.0 mmol/L, 2 h ≥ 8.5 mmol/L |
| Sample size (GDM/non-GDM) | 180 pairs (GDM = 85, control = 95) |
| Infant gestational age in each group | GDM = 38.6 ± 1.0 weeks vs control = 38.9 ± 0.8 weeks ($P = 0.27$) |
| Infant weight in each group | GDM = 3.45 ± 0.40 kg vs control = 3.33 ± 0.36 kg ($P = 0.12$) |
| Delivery type in each group | Cesarean section rate = GDM 53.0% (45/85) vs control 41.1% (39/95) ($P = 0.11$) |
| Timing of microbiome analysis | Meconium collected ≤ 24 h after delivery (before any oral feeding or antibiotic exposure) |
| Sample type | Neonatal meconium samples (+ subset of maternal fecal samples in late pregnancy) |
| Study results (quantitative) | <p>α diversity: Shannon index \downarrow (3.75 ± 0.35 vs 4.17 ± 0.31; $P = 0.001$); Chao1 \downarrow (178.6 ± 28.4 vs 205.2 ± 32.9; $P = 0.004$).</p> <p>β diversity: Significant group separation (Bray-Curtis PERMANOVA $R^2 = 0.062$; $P = 0.001$).</p> <p>Phylum composition (%): <i>Proteobacteria</i> \uparrow (61.2 vs 43.7), <i>Firmicutes</i> \downarrow (25.9 vs 31.8), <i>Bacteroidetes</i> \downarrow (8.5 vs 16.9), <i>Actinobacteria</i> \uparrow (4.4 vs 3.0).</p> <p>Genus abundance (%): \uparrow <i>Escherichia-Shigella</i> (25.2 vs 10.9) and <i>Klebsiella</i> (8.4 vs 3.7); \downarrow <i>Bacteroides</i> (3.8 vs 11.5) and <i>Faecalibacterium</i> (1.9 vs 4.7).</p> <p>Functional features (KEGG): Butyrate metabolism \downarrow 39%, propionate biosynthesis \downarrow 33%, LPS biosynthesis \uparrow 28%, oxidative stress genes \uparrow 22% (all $P < 0.01$).</p> <p>Metabolomic profile ($\mu\text{mol/g}$ meconium): Acetate 22.0 ± 5.2 vs 31.0 ± 5.8 ($P = 0.002$); Propionate 4.9 ± 1.1 vs 6.8 ± 1.7 ($P = 0.003$); Butyrate 5.7 ± 1.5 vs 7.9 ± 2.0 ($P = 0.004$); Glycocholic acid \downarrow 26%; Taurine \uparrow 32%.</p> |

GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; IADPSG: International Association of Diabetes and Pregnancy Study Groups.

of “inflammatory dysbiosis” already evident at birth (27). Lipopolysaccharide (LPS)-rich bacteria such as *Escherichia-Shigella* can activate Toll-like receptor-4 (TLR4), triggering NF- κ B (nuclear factor kappa B)-mediated cytokine release and sustained inflammatory signaling. This early inflammatory priming may lay the foundation for persistent low-grade inflammation and insulin resistance later in life (28).

The concurrent depletion of key SCFA producers, particularly *Bacteroides* and *Lactobacillus*, further highlights the metabolic consequences of GDM-related dysbiosis. SCFAs such as acetate, propionate, and butyrate serve critical roles in maintaining intestinal barrier integrity, suppressing inflammatory cascades, and modulating energy metabolism (29). KEGG pathway analyses in these studies demonstrated down-regulation of SCFA biosynthesis pathways, suggesting a functional metabolic deficiency within the neonatal gut. Insufficient SCFA availability may impair epithelial tight-junction formation by reducing the expression of ZO-1, Occludin, and Claudin-1, thereby increasing gut permeability and exposure to microbial antigens, as the conditions that can exacerbate systemic inflammation (30). Moreover, the observed decrease in pathways related to vitamin B synthesis and lipid metabolism indicates a broader disruption of microbial functional networks essential for early growth and host energy homeostasis (21).

From a mechanistic perspective, maternal hyperglycemia contributes to oxidative stress, inflammatory signaling, and dysregulated cross-talk between maternal and fetal microbiota (31). Alterations in maternal microbial composition and metabolite production may restrict microbial transfer across the placenta, resulting in an underdeveloped and pro-inflammatory neonatal microbiome (32). This impaired microbial inheritance may divert neonatal immune differentiation away from regulatory pathways (Treg) toward Th1 and Th17 profiles, favoring persistent inflammation and diminished immune tolerance (33).

The marked enrichment of LPS biosynthesis and oxidative stress pathways, documented in functional analyses, provides molecular confirmation of a shift toward an inflammatory microbial phenotype (34). Chronic exposure to pro-oxidant metabolites can disrupt mitochondrial function, inhibit mucosal defense gene expression, and amplify cytokine production, including IL-6 and CRP, thereby fueling systemic inflammation. Collectively, these mechanisms depict a neonatal gut environment characterized by compromised epithelial integrity, oxidative stress, and immune hyperactivation, which may collectively increase long-term susceptibility to obesity, insulin resistance, and metabolic disorders (26).

Conclusion

This systematic review demonstrates that GDM profoundly influences the initial microbial and metabolic

environment of the newborn. Across all included studies, neonates born to mothers with GDM exhibited reduced microbial diversity, enrichment of Gram-negative and lipopolysaccharide-producing bacteria, and depletion of beneficial SCFA producers. Functional analyses consistently indicated impaired SCFA biosynthesis, increased inflammatory and oxidative stress pathways, and weakened intestinal barrier integrity. Collectively, these findings suggest that maternal hyperglycemia triggers early-life dysbiosis that may predispose offspring to metabolic inflammation and insulin resistance, forming a critical mechanistic link between intrauterine glucose exposure and future metabolic disease risk.

Limitations of the study

Variation in sequencing platforms, data analysis pipelines, and bacterial taxonomic classification methods across studies represents a major limitation of this research. Such heterogeneity can substantially affect accuracy, comparability, and the interpretation of results. Differences in the technologies used to identify and classify microbial species, particularly at the gene or sequence level may lead to discrepancies in relative abundance and diversity estimates, thereby altering the true assessment of neonatal gut microbiota composition.

Authors' contribution

Conceptualization: Mohammad Hosein Atarod.

Data curation: Leila Zakeri Rad and Sahar Bagheri Chime.

Formal analysis: Leila Zakeri Rad.

Investigation: Mohammad Hosein Atarod.

Methodology: Leila Zakeri Rad, Mohammad Hosein Atarod.

Project management: Elina Bairamzadeh and Sahar Bagheri Chime.

Resources: Elina Bairamzadeh.

Supervision: Elina Bairamzadeh.

Validation: Elina Bairamzadeh.

Visualization: Leila Zakeri Rad and Sahar Bagheri Chime.

Writing—original draft: All authors.

Writing—review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this manuscript, Grammarly was used solely to improve English grammar and language accuracy. The authors subsequently reviewed and edited the manuscript and assume full responsibility for its content.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD420251236989). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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