



Original Article

Diversity and Composition of the Adult Fecal Microbiome Associated with History of Cesarean Birth or Appendectomy: Analysis of the American Gut Project

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ABSTRACT

Background: Cesarean birth is associated with altered composition of the neonate's microbiota and with increased risk for obesity and other diseases later in life. The mechanisms of these associations, and whether cesarean birth is associated with an altered adult microbiota, are unknown.

Methods: In 1097 adult volunteers without diabetes, inflammatory bowel disease, or recent antibiotic use, fecal microbiome metrics were compared by history of cesarean birth (N = 92) or appendectomy (N = 115). Associations with potential confounders, microbiome alpha diversity, and individual microbial taxa were estimated by logistic regression. Permutation tests assessed differences in microbial composition (beta diversity) based on Jensen–Shannon divergence.

Findings: Cesarean birth history was associated with younger age; appendectomy with older age and higher body mass index. Neither was associated with fecal microbiome alpha diversity. Microbial composition at all taxonomic levels differed significantly with cesarean birth ($P \leq 0.008$) but not with appendectomy ($P \geq 0.29$). Relative abundance differed nominally for 17 taxa with cesarean birth and for 22 taxa with appendectomy, none of which was significant with adjustment for multiple comparisons.

Interpretation: Adults born by cesarean section appear to have a distinctly different composition of their fecal microbial population. Whether this distinction was acquired during birth, and whether it affects risk of disease during adulthood, are unknown.

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1. Introduction

Prenatal and early postnatal exposures and events can affect the entire life course. As one example, cesarean birth has been associated with an increased likelihood of asthma and cardiovascular disease in children (Renz-Polster et al., 2005; Thavagnanam et al., 2008; Friedemann et al., 2012), hypertension in young adults (Horta et al., 2013), and obesity in both children and adults (Pei et al., 2014; Darmasseelane et al., 2014; Blustein et al., 2013; Mueller et al., 2014). While these associations are certainly multifactorial, differences in the gut microbiota could contribute. As well summarized by Arrieta and colleagues, several studies have noted differences in the neonatal fecal microbiota by route of delivery (Arrieta et al., 2014). Using aerobic and anaerobic cultures, Adlerberth et al. found higher abundance of *Escherichia coli* and lower abundance of enterobacteria in 99 vaginally delivered compared 17 cesarean delivered newborns (Adlerberth et al., 2006). Biasucci et al. used PCR amplification of *Bifidobacterium* species as

well as PCR-denaturing gradient gel electrophoresis to find that 23 cesarean-delivered newborns had lower bacterial diversity and an absence of *Bifidobacteria* compared to 23 vaginally delivered newborns (Biasucci et al., 2008). Among 1032 infants studied at age 1 month, Penders and colleagues used polymerase chain reaction to quantify total bacteria and five bacterial taxa, finding that cesarean birth was associated with higher carriage of *Clostridium difficile* and lower abundance of *Bacteroides* and *Bifidobacteria* (Penders et al., 2006), thereby confirming Biasucci et al. (2008). More recently, with comprehensive analysis based on next generation sequencing of 16S rRNA genes, Dominguez-Bello and colleagues reported that route of delivery was associated with differences in the composition of the microbial populations that initially colonized the offspring. Notably, neonates who were born vaginally were colonized by vagina-associated bacteria, whereas those born by cesarean section were initially colonized by skin-associated bacteria (Dominguez-Bello et al., 2010).

Early life alteration of the gut microbiota may have a lasting effect. Trasande et al. observed that exposure to antibiotics up to age 6 months was associated with elevated body mass index (BMI) up to age 7 years (Trasande et al., 2013). In a recently reported murine model, Cox and colleagues observed that prenatal and postnatal exposures to

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subtherapeutic doses of penicillin resulted in an alteration of the gut microbiota that was transient (Cox et al., 2014). However, the early life exposure to penicillin also caused prolonged metabolic alterations including exacerbated diet-induced obesity (Cox et al., 2014). These observations are consistent with studies in humans showing that the distal gut microbial population may have a major effect on the risks for obesity and malnutrition. Among American adults, the composition of the microbial population in feces is generally altered with obesity, with enrichment by taxa in the phylum Firmicutes (Turnbaugh et al., 2009). Conversely, Malawian infants and young children with Kwashiorkor also have an altered population of fecal microbes, without a clear taxonomic signature but with a disease phenotype that could be transmitted by transplantation of Kwashiorkor feces to gnotobiotic mice (Smith et al., 2013). Likewise, the penicillin-induced obesity phenotype in the mouse could be transferred by fecal transplantation (Cox et al., 2014).

If cesarean delivery has a prolonged effect on the microbiota, this could contribute to the risk for metabolic diseases later in life. Herein, we explored whether the fecal microbiota differs between adults who reported that they were born by cesarean versus vaginal delivery. For comparison, in the same population we looked for differences in the fecal microbiota with history of appendectomy (Guinane et al., 2013; Randal Bollinger et al., 2007). The appendix, particularly its microbial-rich biofilm, has long been postulated to serve as a repository for repopulating the distal gut following an insult such as diarrheal disease or antibiotic exposure (Randal Bollinger et al., 2007). Whether and how this occurs is unknown, particularly in light of a recent observation that surgically removed appendices contained some taxa that are infrequently found in the distal gut (Guinane et al., 2013). In either case, removal of the appendix could result in a persistent alteration of the fecal microbiota.

2. Methods

The 16S rRNA V4 region was sequenced by the American Gut Project. The operational taxonomic unit (OTU) table rarefied to 10,000 sequence reads per sample, as well as metadata, was downloaded from the American Gut Project website (<https://github.com/biocore/American-Gut/tree/master/data/AG>). A current summary is available at http://microbio.me/AmericanGut/static/img/mod1_main.pdf, and details of the OTU picking and taxonomy assignment are available at http://nbviewer.ipynb.org/github/biocore/American-Gut/blob/master/ipynb/module2_v1.0.ipynb. Alpha diversity (number of OTUs, Shannon's index, Chao1, Phylogenetic diversity_whole tree), UniFrac distance matrix and relative abundance of different taxa were calculated in the Quantitative Insights Into Microbial Ecology (QIIME) pipeline.

2.1. Data Cleaning and Exclusions

In the full data set, there were 1962 samples, 174 phenotypic variables and 3599 taxa with relative abundance. Among those, 1134 samples were left after exclusions [age <4 years (number removed, 121), sex missing (196), race missing (19), specimen not feces (393), used antibiotic in the past month (131), has diabetes (107) or inflammatory bowel disease (170)]. After that, 37 duplicated samples were also removed. The remaining 1097 samples were used for statistical analysis (1040 for cesarean associations, and 1076 for appendectomy associations).

2.2. Covariate Tests

We used logistic regression to test the association between history of cesarean birth (CSECTION in the data set) and the following variables: age, race/ethnicity, sex, geographic region, BMI, weight change, diet type, gluten sensitivity (GLUTEN), lactose intolerance (LACTOSE), asthma, and frequencies of smoking and alcohol consumption. The

logistic regression was repeated with history of appendectomy (APPENDIX_REMOVED) as the dependent variable and the same dependent variables.

2.3. Alpha Diversity and Individual Taxa Tests

We used logistic regression to test associations of case status (cesarean birth or appendectomy) with richness, standard estimates of alpha diversity (Shannon, Chao 1, inverse Simpson, and phylogenetic distance whole tree indices) and each of the 1949 taxa in the 1097 samples, adjusting for age, sex and race/ethnicity. The Wald test was used to calculate P values as the primary test. Significance after false discovery rate (FDR) adjustment for multiple comparisons was also considered.

2.4. Clustering Analysis and Testing

As used previously to define and test associations with clusters of the microbiome in the vagina (Gajer et al., 2012), our primary analysis was based on Jensen–Shannon (J–S) divergence at each taxonomic level from phylum down to species. For K taxa at a given level, let $P^i = (p_1^i, \dots, p_K^i)$ denote the relative abundances for subject i . The Kullback–Leibler (K–L) divergence between subject i and j is defined as $D_{KL}(P^i|P^j) = \sum_{k=1}^K p_k^i \log(p_k^i/p_k^j)$ with respect to the distribution of subject i . Since the K–L divergence is not symmetric, we calculated the J–S divergence as the distance between the pair (i, j) , defined as $JSD(P^i, P^j) = (D_{KL}(P^i|Q_{ij}) + D_{KL}(P^j|Q_{ij}))/2$, where the vector $Q_{ij} = (P^i + P^j)/2$ represents the average distribution of microbiome community i and j . Based on the J–S divergence matrix, we also performed hierarchical clustering. Based on the distance matrix, we performed permutation tests to investigate whether the case group (cesarean birth or appendectomy) was significantly clustered relative to the whole set of samples.

2.5. Role of the Funding Source

The funding source had no direct role in study design, data collection, data analysis, interpretation, or writing the report.

3. Results

Of the 1097 participants, cesarean birth was reported as “yes” by 92, “no” by 948, and missing or uncertain by 57. Likewise, appendectomy was reported as “yes” by 155, “no” by 961, and missing or uncertain by 21. Selected characteristics of the participants and associations with cesarean birth and appendectomy history are presented in Table 1. The population in the cesarean birth analysis was 44% male, 93% non-Hispanic Caucasian, and distributed through all U.S. regions. They had a mean age of 46 [standard error (SE) 16] years and a mean BMI of 24 (SE 5). An omnivorous diet was reported by 80%, gluten sensitivity by 19%, and lactose sensitivity by 18%. Weight loss of at least 10 lb was reported by 10% and weight gain by 5%. An antibiotic had been used by 11% 2–6 months and 13% 7–12 months before participation. Cesarean birth was significantly associated with younger age, but not consistently with any of the other characteristics. History of appendectomy was significantly associated with older age and with higher BMI, and it tended to be more frequent in U.S. states outside California. Without adjusting for age or any other characteristic, cesarean birth and appendectomy histories had a weak inverse association ($P = 0.11$).

In the 1097 fecal specimens, taxa were mapped to 261 bacterial families, 626 genera, and 844 species. Microbiome richness and alpha diversity estimates were not associated with cesarean birth or appendectomy history (Supplemental Table 1). In contrast, composition (beta diversity) of the fecal microbiome differed significantly for participants who reported cesarean birth. Average J–S divergence was

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