Effects of formula supplementation on the composition of the infant microbiome

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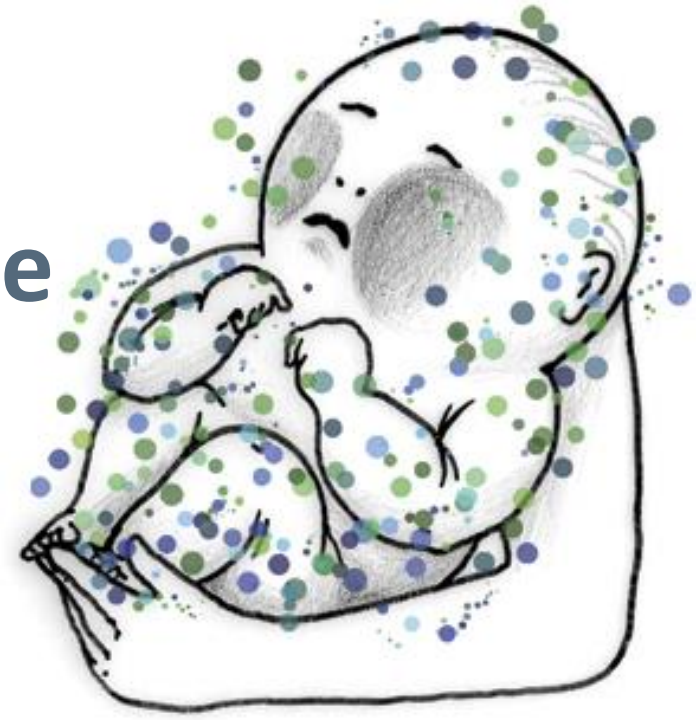


Genetic Science Learning Center
University of Utah
http://learn.genetics.utah.edu

The human microbiome

- The “forgotten organ”
- **Co-evolved with humans**
- 100 trillion organisms in the intestine
- 1000 species Qin J et al. 2010
- 10 microbes for every human cell
- 100 microbial gene for every human gene
- Innate and adaptive immunity evolved to *require* microbial interactions during development Lee YK et al. 2010, Chow et al. 2010

Consequences for health

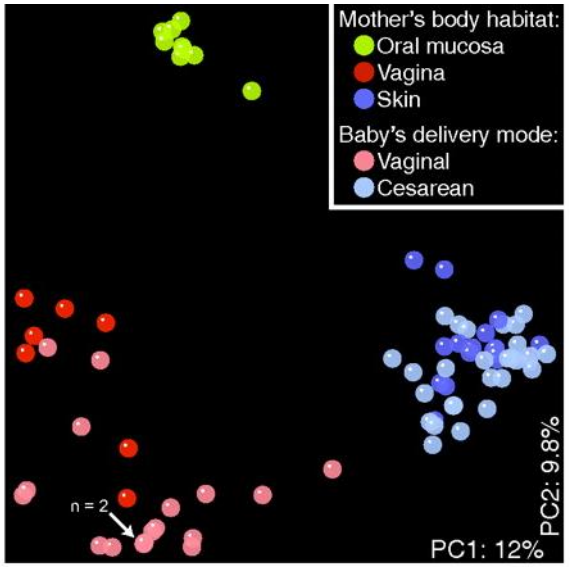
- Out-competing pathogens
- Conferring resistance to infection (Gill et. al. 2012, Britton and Young 2012, Olszak et. al. 2012)
- Reducing susceptibility to inflammatory and metabolic disorders (Frank et. al. 2011, Nieuwdorp et. al. 2014)
  - Microbial diversity in the *first weeks of life* related to allergy at school age (Wang et al. 2008; Bisgaard et al. 2011)

The microbiome at birth

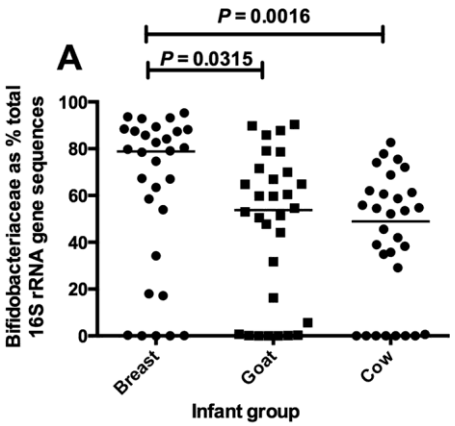
- Recent evidence points to some exposure of fetus to microbes through placenta, umbilical cord and/or amniotic fluid (Jiménez et. al. 2007, Aagaard et. al. 2014)
- Major colonization event at birth
  - Vaginal microbiome shifts during pregnancy to become dominated by *Lactobacillus* (Aagaard et. al. 2012)
  - Human milk oligosaccharides promote the proliferation of *Bifidobacterium infantis* in infant intestinal tract (Coppa et. al. 2004)

Delivery mode and feeding

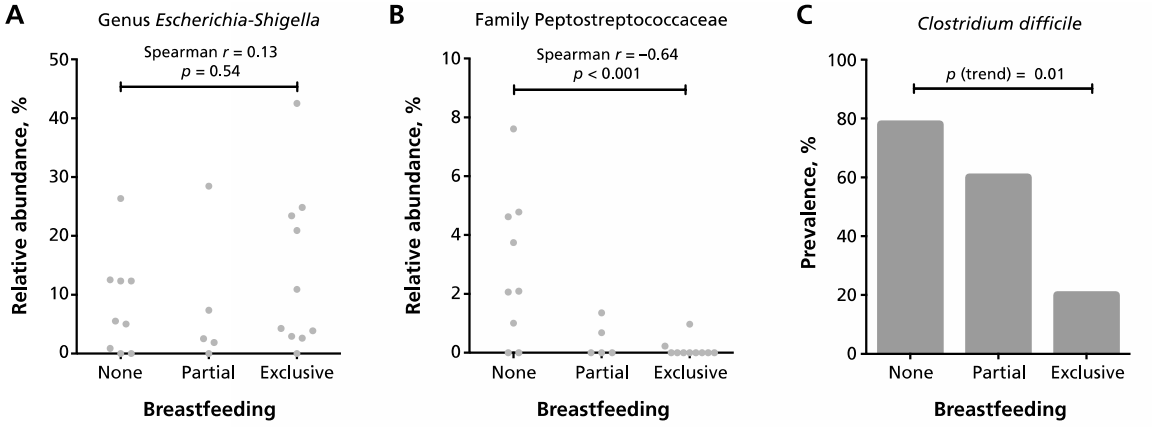
Feeding method (breast milk vs formula) and delivery mode (vaginal vs. C-section) are the most commonly found correlates of microbiome composition in young infants



Maria G. Dominguez-Bello et al. 2010



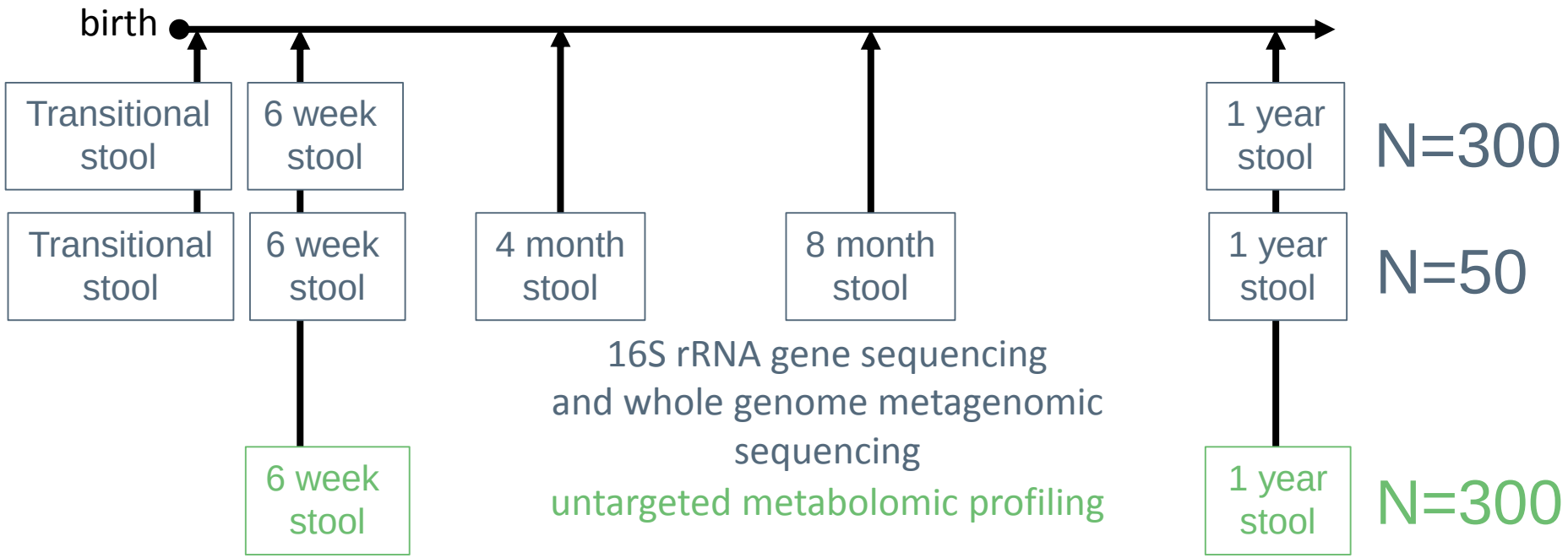
Tannock et. al. 2013



Azad et. al. 2013

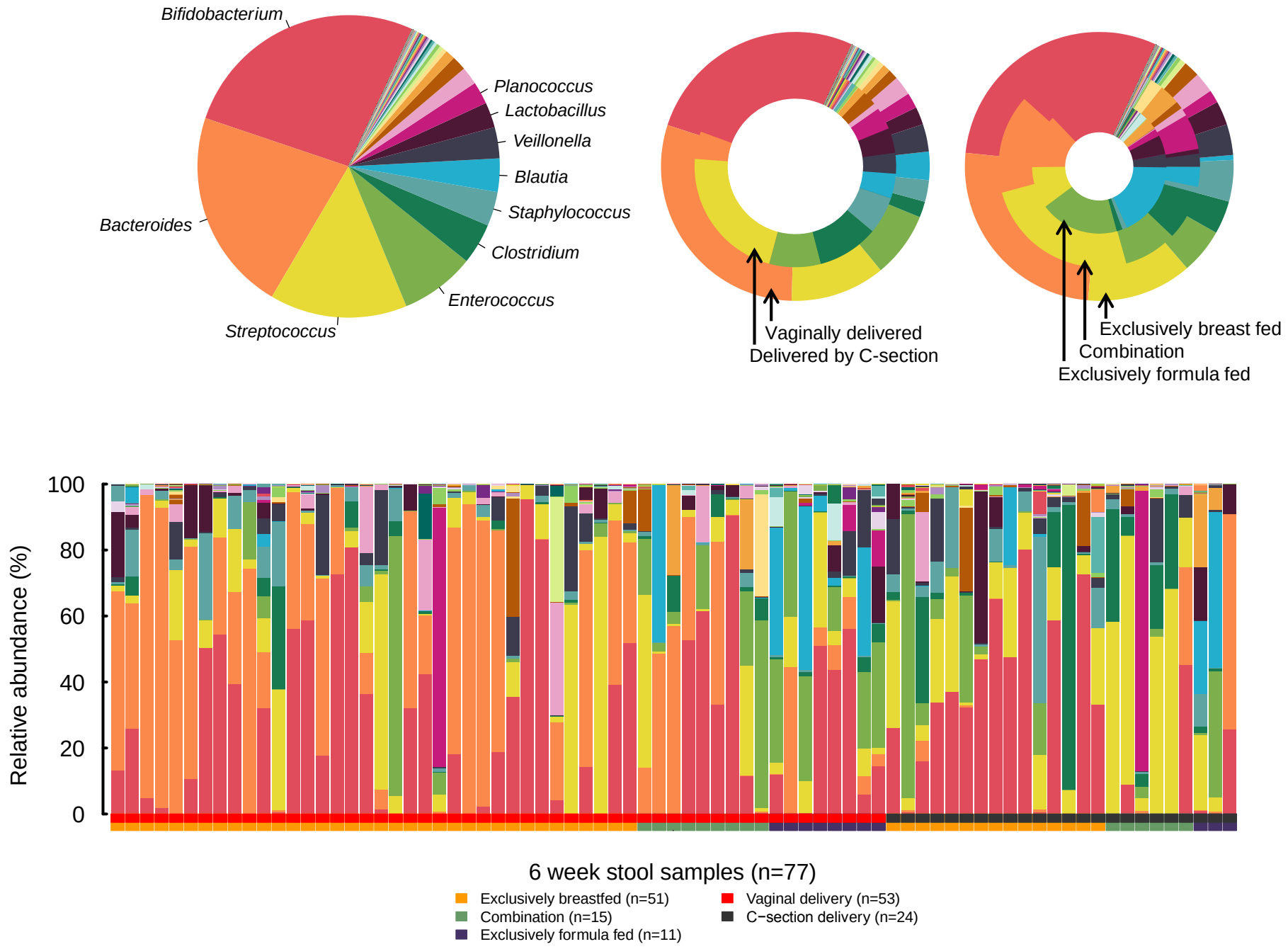
New Hampshire Birth Cohort Study

- 1500 mothers who used a private well enlisted during 2nd trimester of pregnancy
- Infant stool collection:

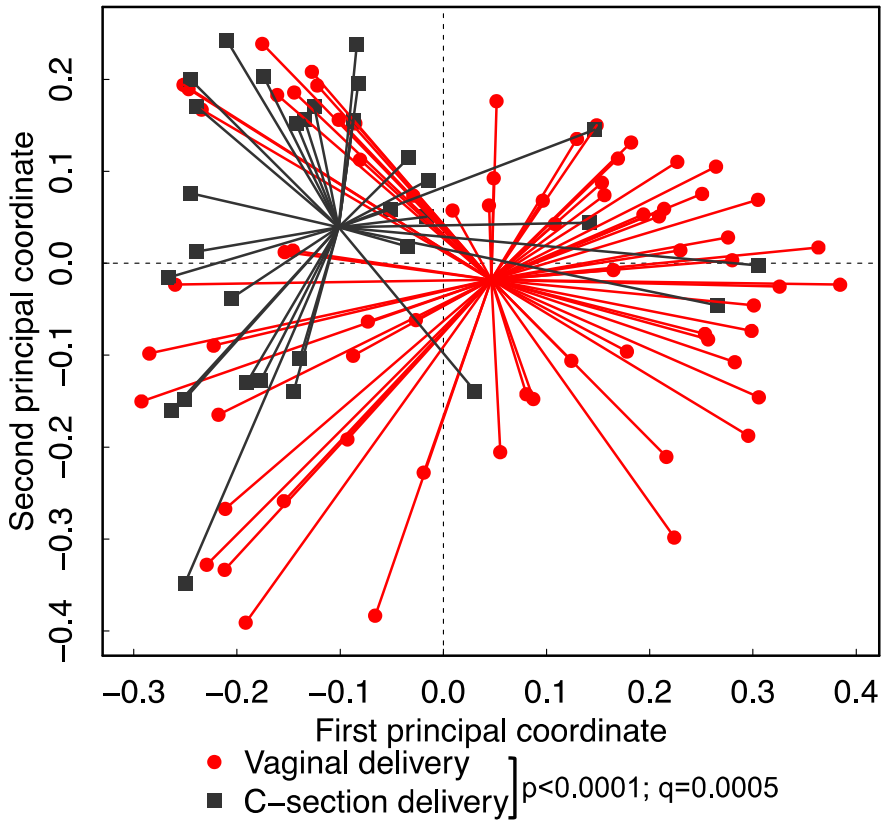


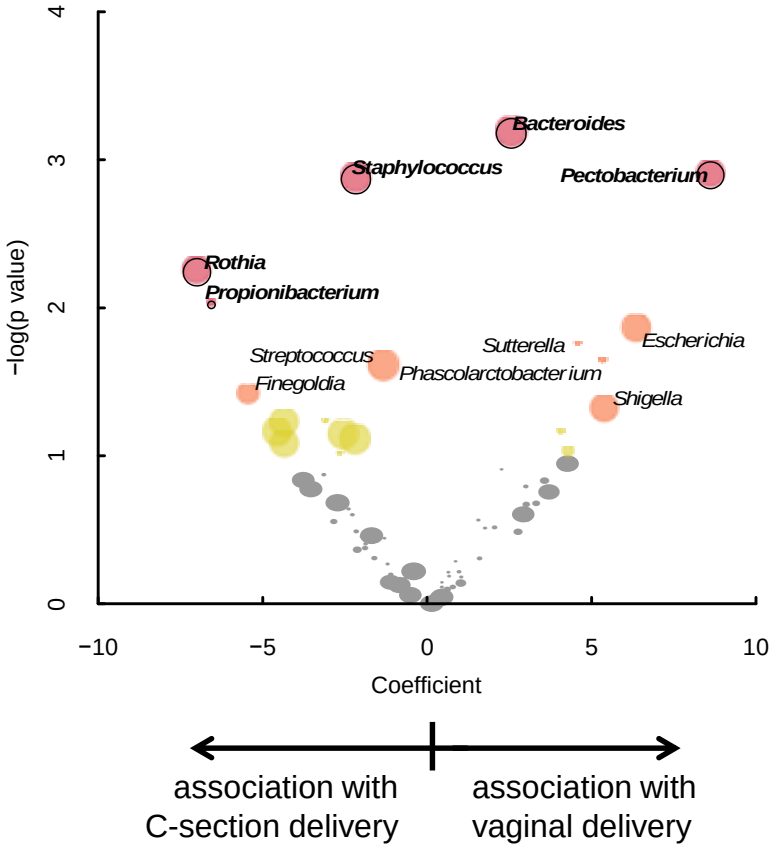
Exposure data

- Delivery mode abstracted from delivery medical record
- Infant feeding over first 6 weeks of life ascertained by follow-up questionnaire
  - Exclusive breast feeding
  - Partial breast feeding (‘combination feeding’)
  - Exclusive formula feeding
- Infant urinary arsenic concentration measured at time of 6 week stool collection


Bifidobacterium
Planococcus
Lactobacillus
Veillonella
Blautia
Staphylococcus
Clostridium
Enterococcus
Streptococcus
Bacteroides
Vaginally delivered
Delivered by C-section
Exclusively breast fed
Combination
Exclusively formula fed
Relative abundance (%)
100
80
60
40
20
0
6 week stool samples (n=77)
Exclusively breastfed (n=51)
Combination (n=15)
Exclusively formula fed (n=11)
Vaginal delivery (n=53)
C−section delivery (n=24)

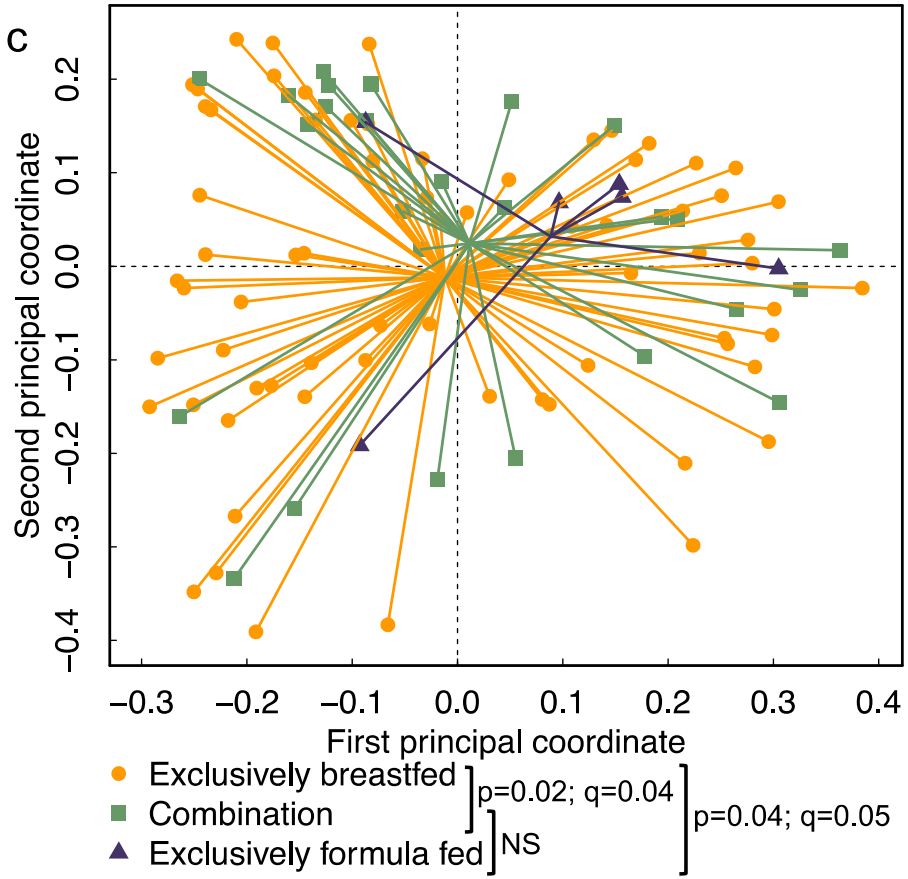
Delivery mode

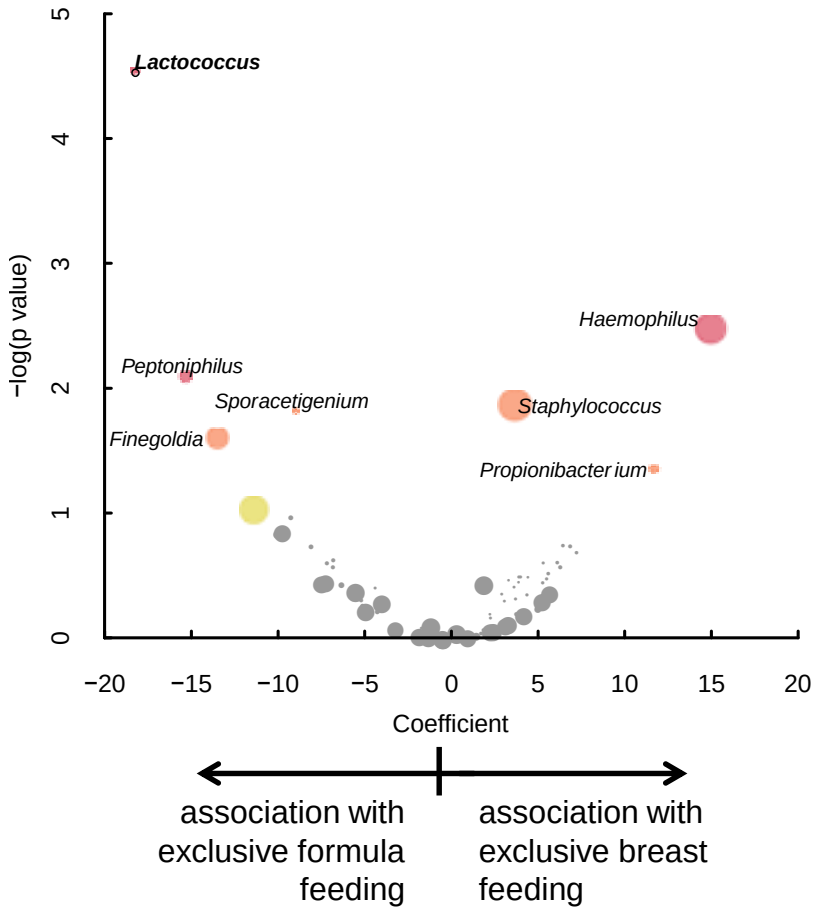




JAMA Pediatrics to appear Jan 11, 2016

Feeding





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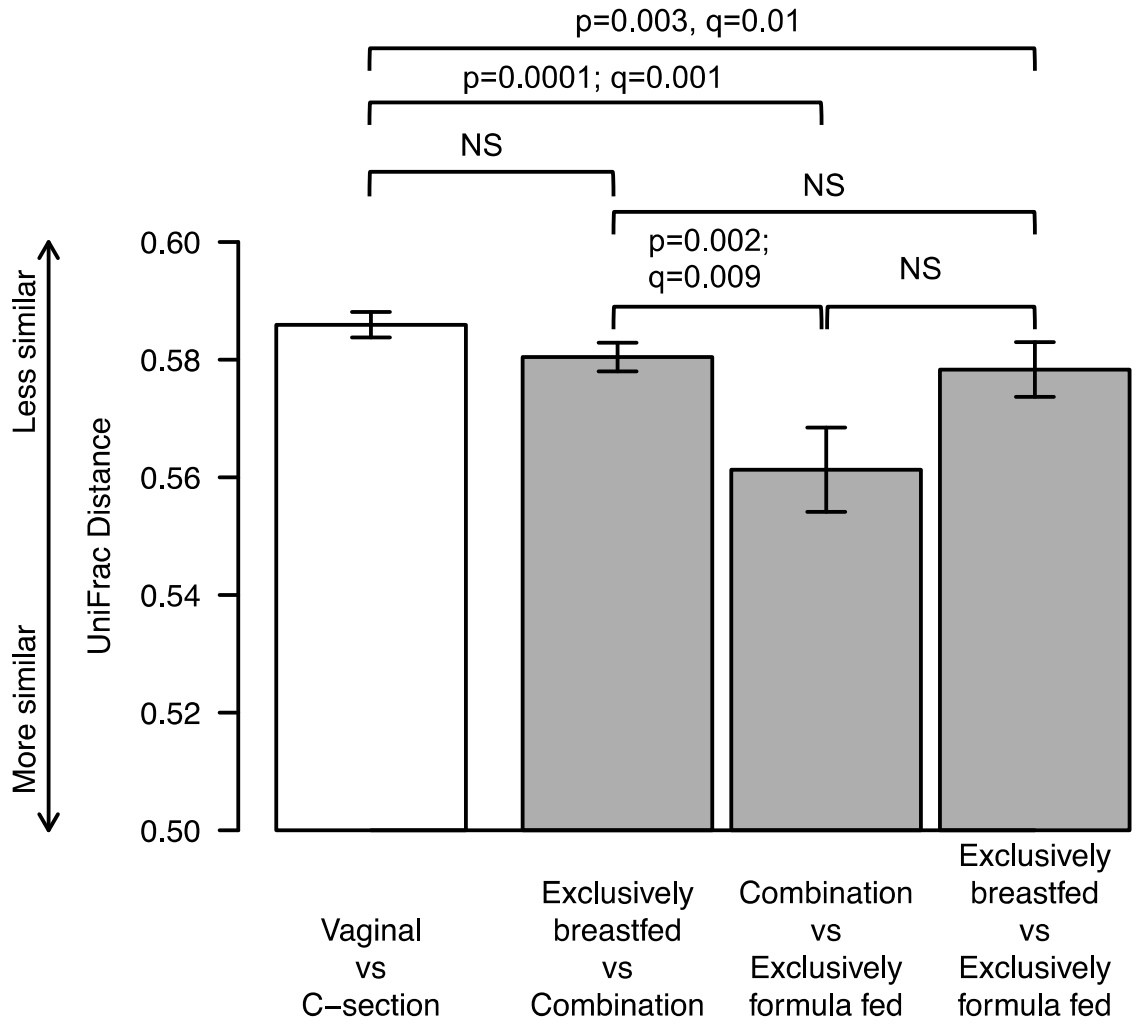
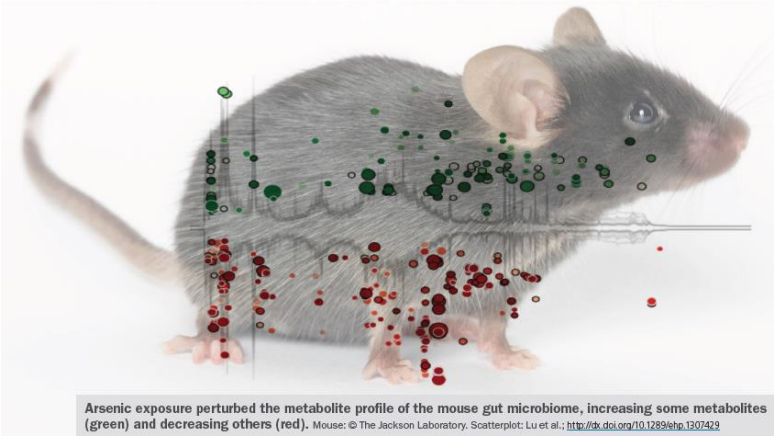
Between-group comparisons



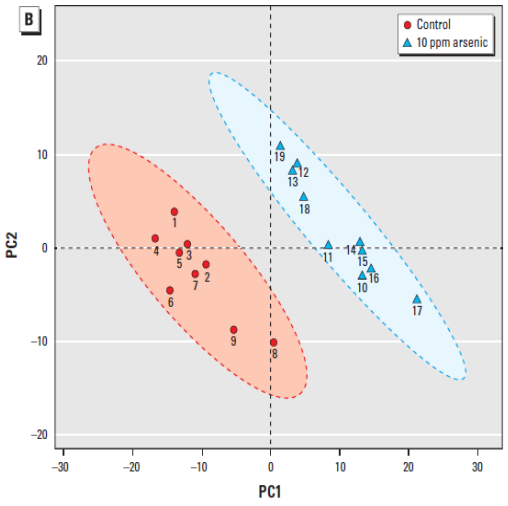
JAMA Pediatrics to appear Jan 11, 2016

Arsenic and the microbiota

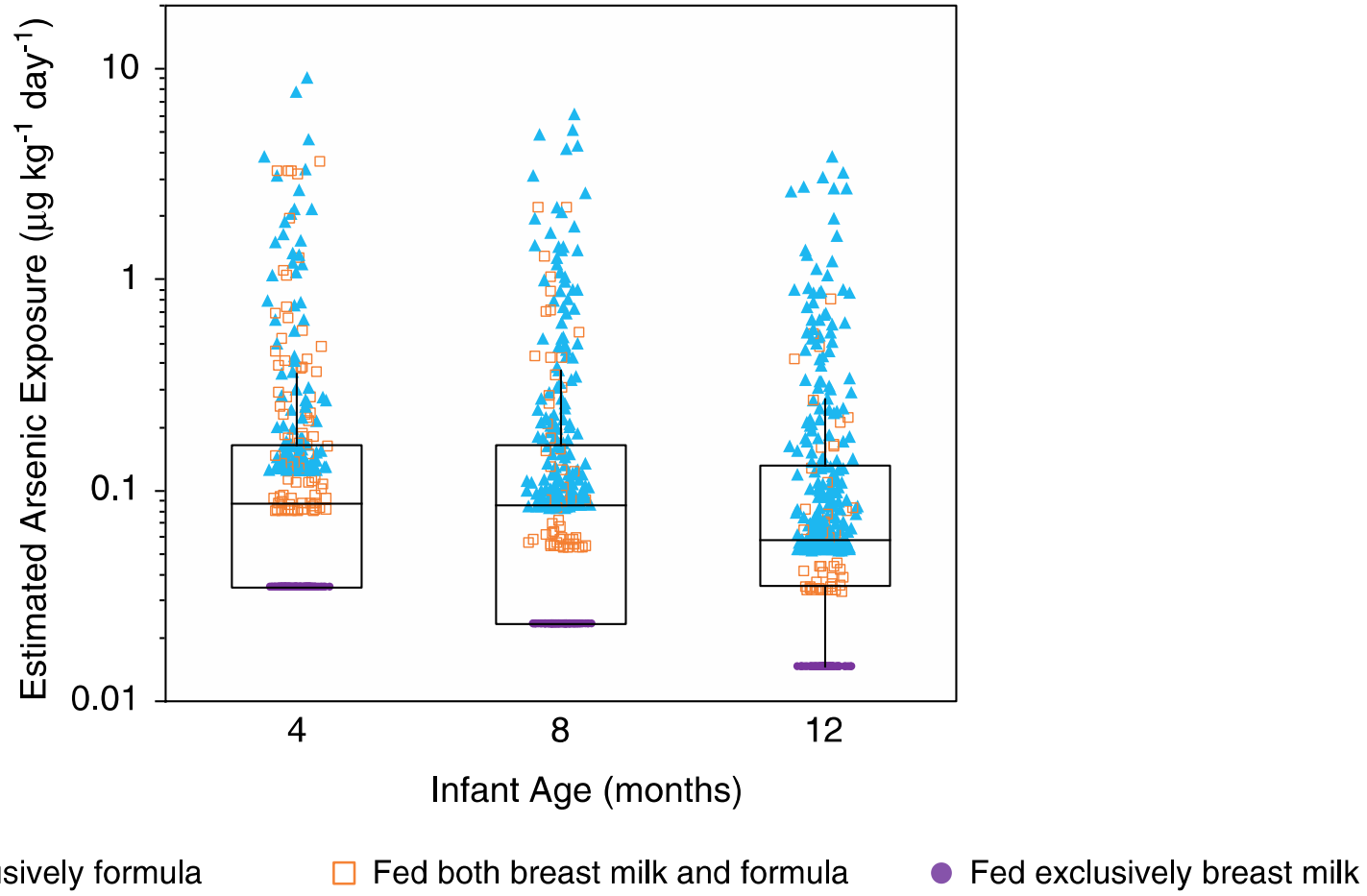
- Mouse model: 10 ppm As for 4 weeks in drinking water Lu et al. 2014
- As significantly perturbs the gut microbiome composition
- Metabolomics revealed metabolites perturbed



Arsenic exposure perturbed the metabolite profile of the mouse gut microbiome, increasing some metabolites (green) and decreasing others (red). Mouse: © The Jackson Laboratory. Scatterplot: Lu et al.; http://dx.doi.org/10.1289/ehp.1307429



NHBCS arsenic exposure model



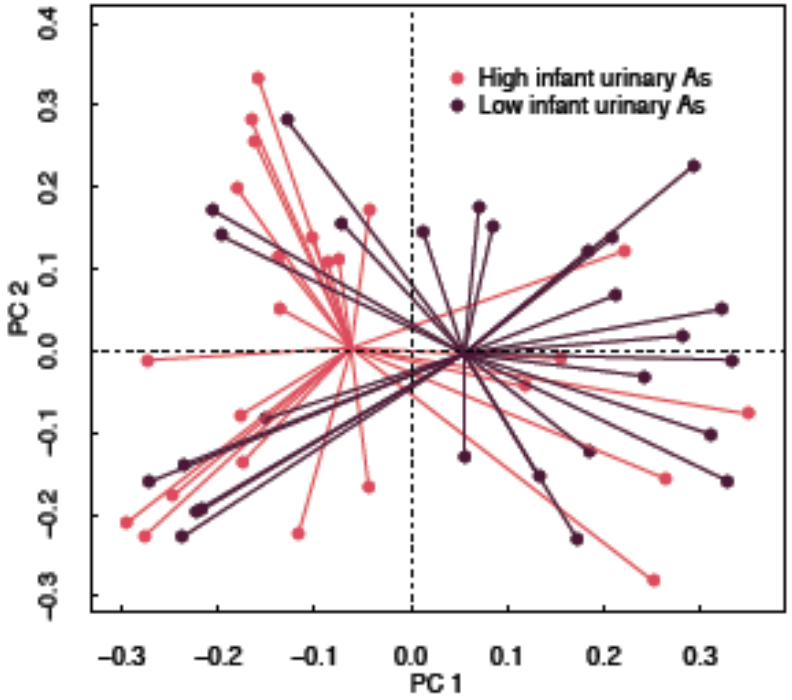
Carignan, Karagas et al. 2015

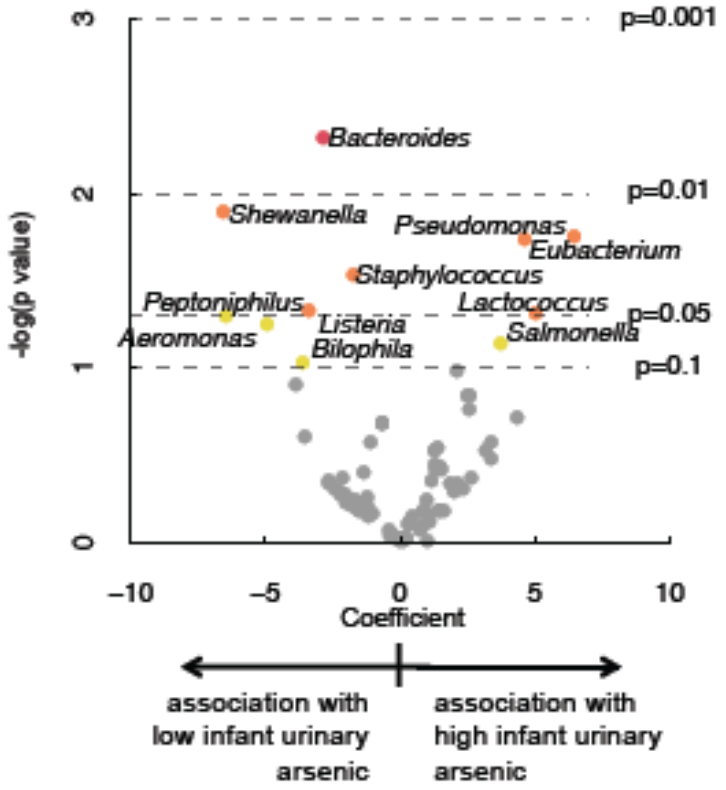
Infant Urinary Arsenic

Significant association between microbiome composition
and
ln(infant urinary arsenic concentration) p=0.006

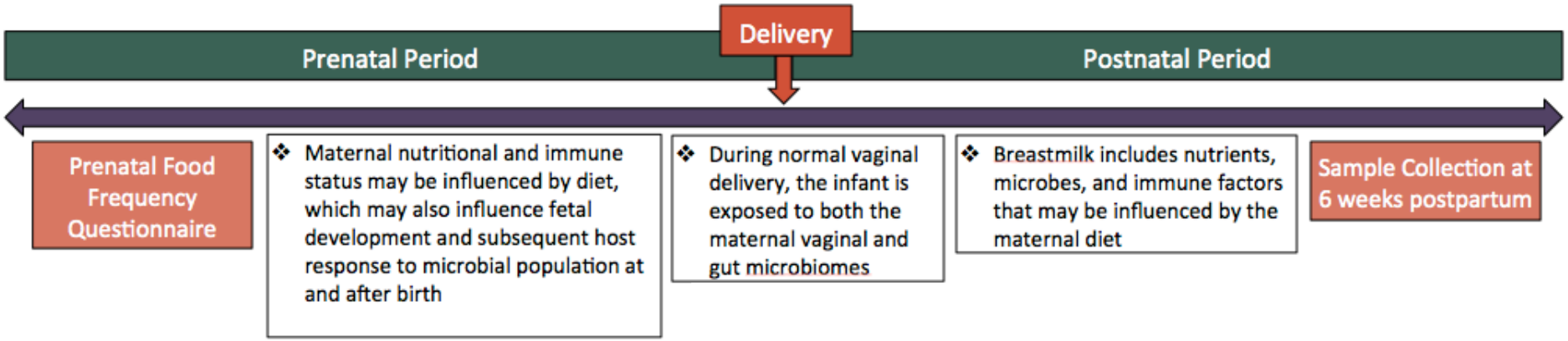
Among exclusively breast fed infants p=0.38

Among formula fed infants p=0.009

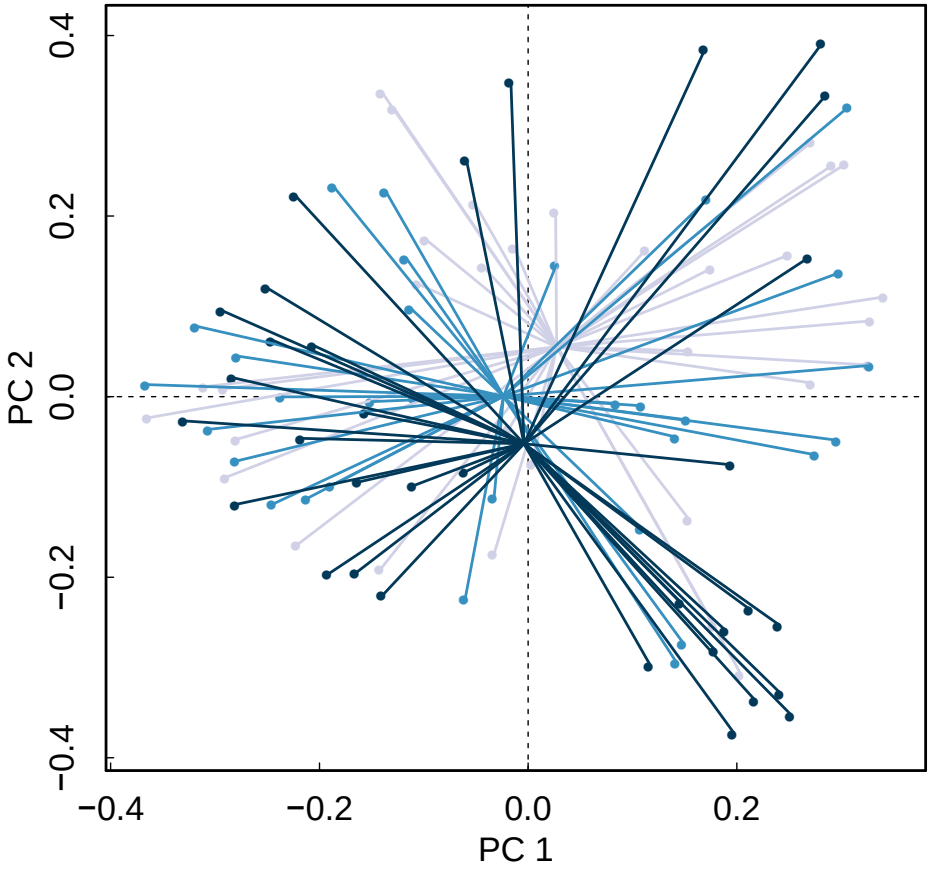




Maternal diet



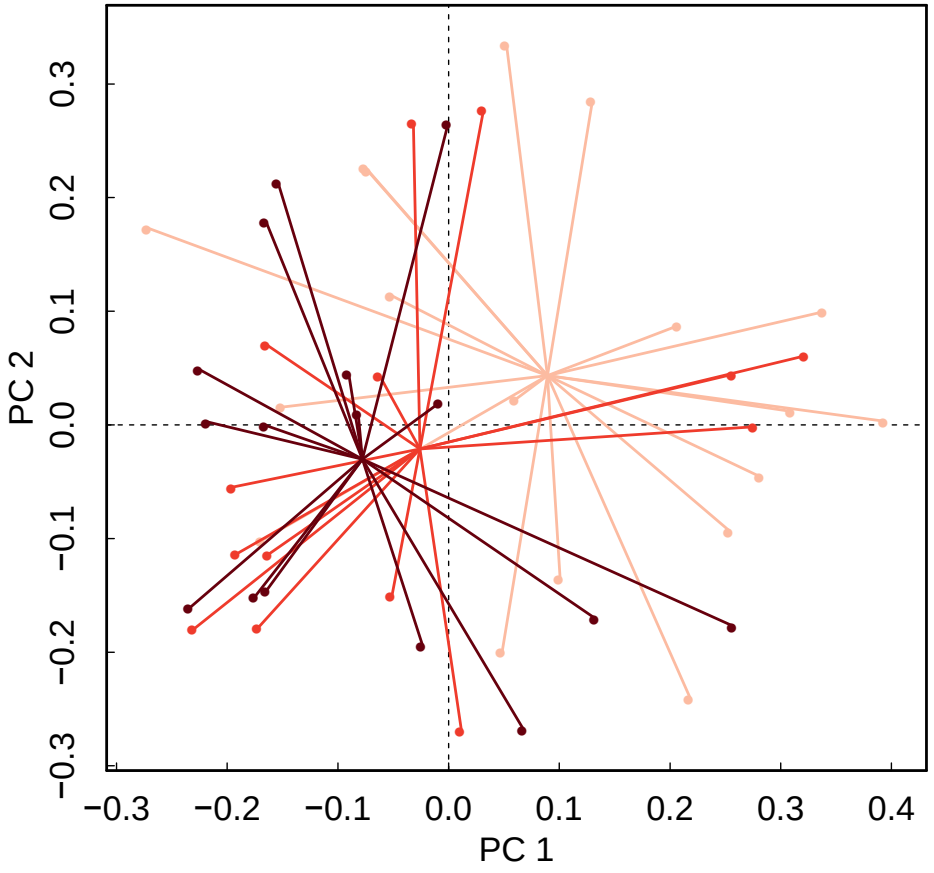
PCoA of Generalized UniFrac Distances Colored by Fruit Consumption Tertiles in Infants Born Vaginally



1st Tertile
2nd Tertile
3rd Tertile

Continuous crude p−value = .04 *
Continuous adjusted p−value = .03 *
Tertile crude p−value = .10
Tertile adjusted p−value = .14

PCoA of Generalized UniFrac Distances Colored by Dairy Consumption Tertiles in Infants Born by Cesarean Section



1st Tertile
2nd Tertile
3rd Tertile

Continuous crude p−value = .04 *
Continuous adjusted p−value = .04
Tertile crude p−value = .007 **
Tertile adjusted p−value = .001 ***

Future plans

- High between-subject variation—need for longitudinal sampling
- Identify other factors important in shaping stool microbiome—likely a wide range
- Metabolomics to understand **functional** associations
- Exposure → microbiota → health outcomes
- Microbe-microbe interactions

THE CHILDREN'S ENVIRONMENTAL HEALTH & DISEASE PREVENTION RESEARCH CENTER AT DARTMOUTH

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