Impact of Milk Sugars and Oligosaccharides on Infant Body Composition, Feeding Behaviors and Cognitive Outcomes

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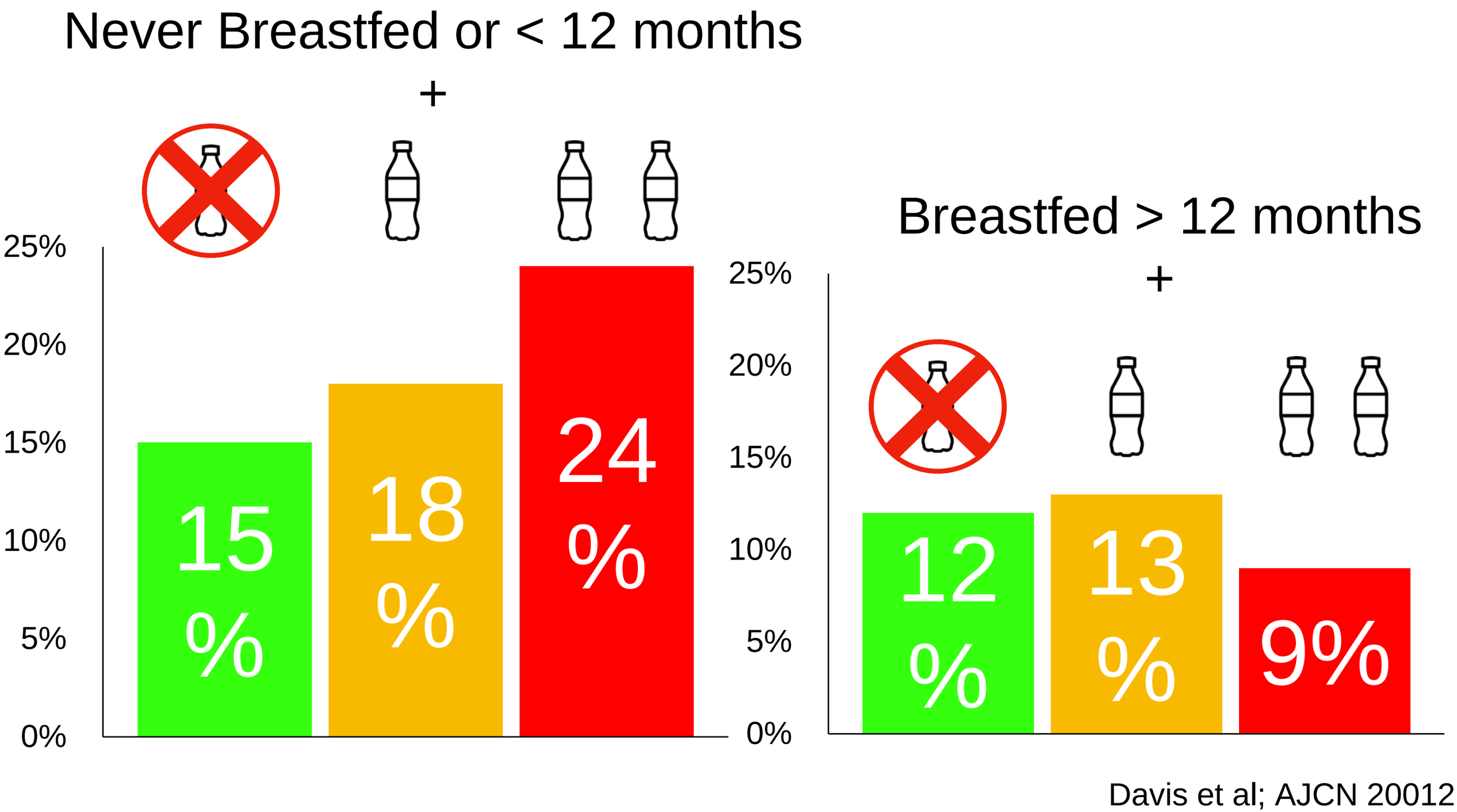
Early Introduction of Sugar Increase Obesity But Extended Breastfeeding Protects from this Adversity



Davis et al; AJCN 20012

Sugary Beverage Intake in Second Trimester of Pregnancy Associated With Greater Adiposity in Offspring in Childhood: Project VIVA

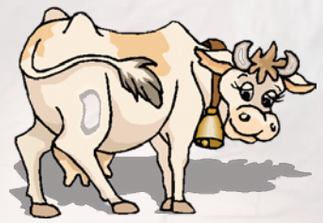
In 1078 mother-child pairs, each 1 serving/day of SSB was associated with increased adiposity:

- BMI z-score: +0.07
- DEXA Fat Mass: 0.15 kg/m^2
- SS + TR skinfolds: 0.85 mm
- Waist circumference: 0.65 cm

- Models adjusted for maternal age, race, education, parity, smoking, pre-pregnancy BMI, household income, and child age and sex
- Effects due to maternal, not child, SSB
- Effects due to sodas & juice drinks - no effects of fruit juice
- No effect of 1st trimester intake

Gillman et al. Pediatrics 2017

MACRONUTRIENTS AND SUGARS IN HUMAN MILK



[g/L]		
Protein	**12**	**35**
Fat	**35**	**35**
Lactose	**65**	**45**
Oligosaccharides	**5-15!**	**0.05**

Lars Bode

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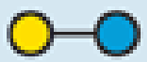
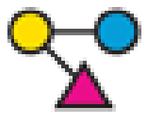
what about other simple sugars like glucose and fructose?

Protective Sugars in Human Breastmilk?
Human Milk Oligosaccharides



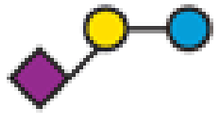
Lactose

The largest nonwater component of breast milk, lactose is digested by the baby. It is also a fundamental building block of the larger oligosaccharides found in breast milk.



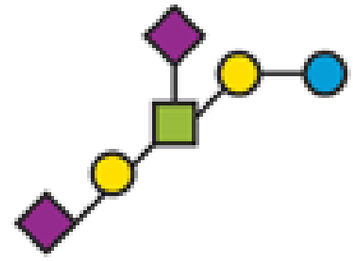
2'-fucosyllactose

This oligosaccharide may fight cholera, *E. coli*, campylobacter infection and other pathogens in the gut.



3'-sialyllactose

By changing the outer landscape of cells that line the gut, 3'SL makes it difficult for troublesome *E. coli* bacteria to bind and linger there, lab tests show.



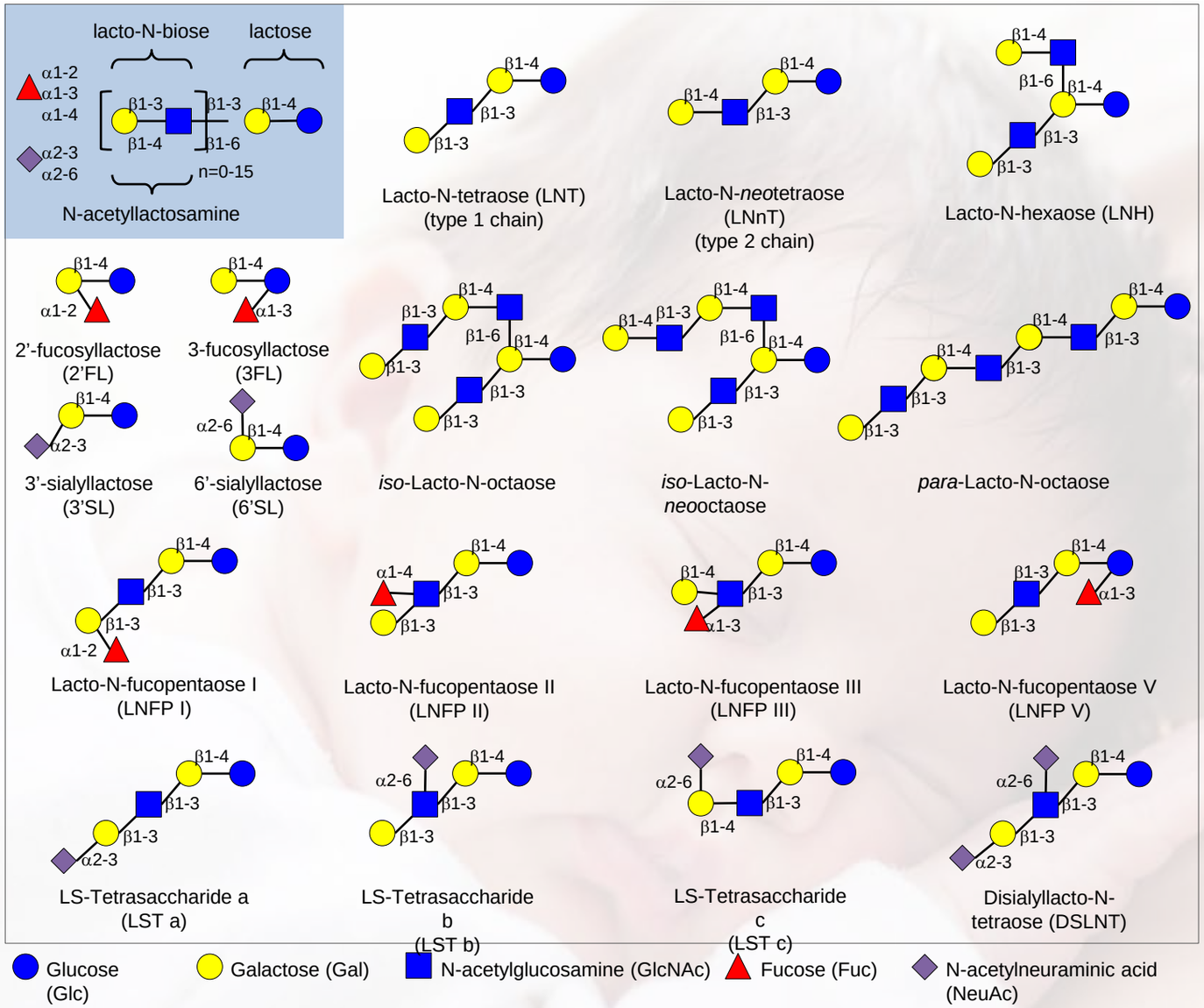
Disialyllacto-N-tetraose

Studies in neonatal rodents show that DSLNT may help prevent a deadly condition common in premature infants called necrotizing enterocolitis.

Galactose Glucose Fucose N-acetylglucosamine N-acetylneuraminic acid

- Complex sugars, high abundance in human milk but profile of different HMOs is highly variable between women (~100 different structures)
- Known to play a key role in developing infant immunity
- 2’FL thought to have an essential role in infant cognitive development
- Also act as prebiotics as they are degraded in the colon and might contribute to shaping gut microbiome which occurs in first 2y of life, and thus obesity development

HMO BLUEPRINT AND STRUCTURAL DIVERSITY



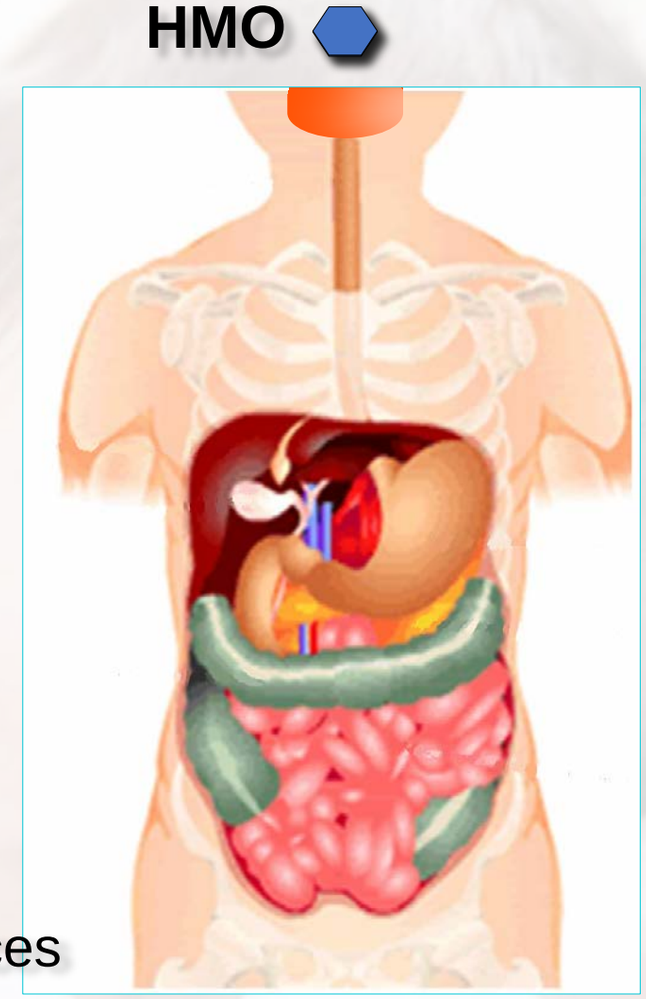
150 – 200 different HMOs

HMO METABOLIC FATE

resistant to
- low pH
- pancreatic and brush border enzymes

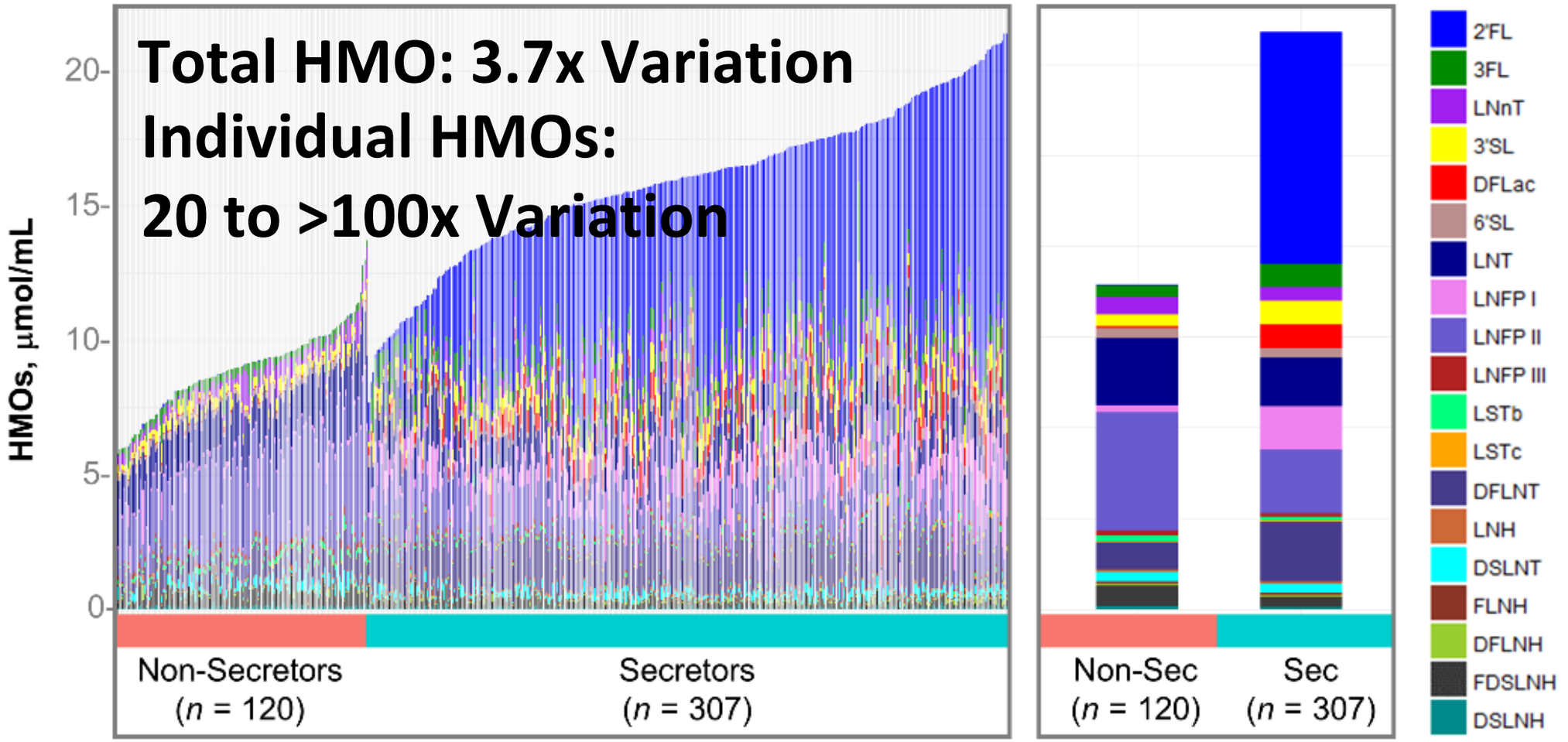
small intestine:
<1% absorbed,
appear in the urine

colon:
bacterial degradation,
10-80% excreted w/ feces



Bode L. *Glycobiology* 2012; 22:1147-62

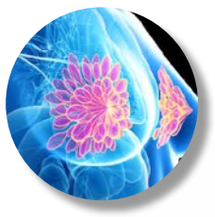
HMOs in the CHILD Cohort in Canada

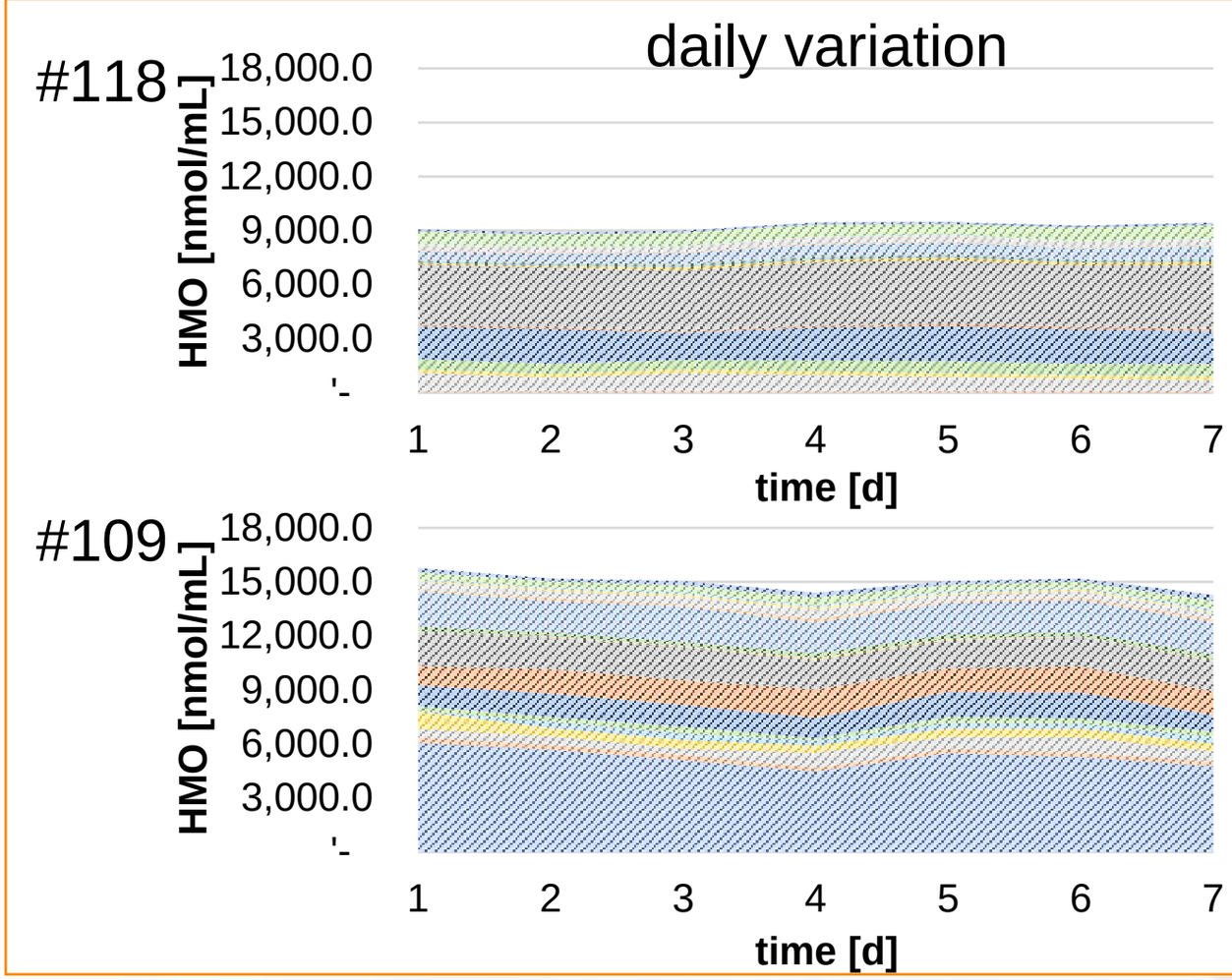


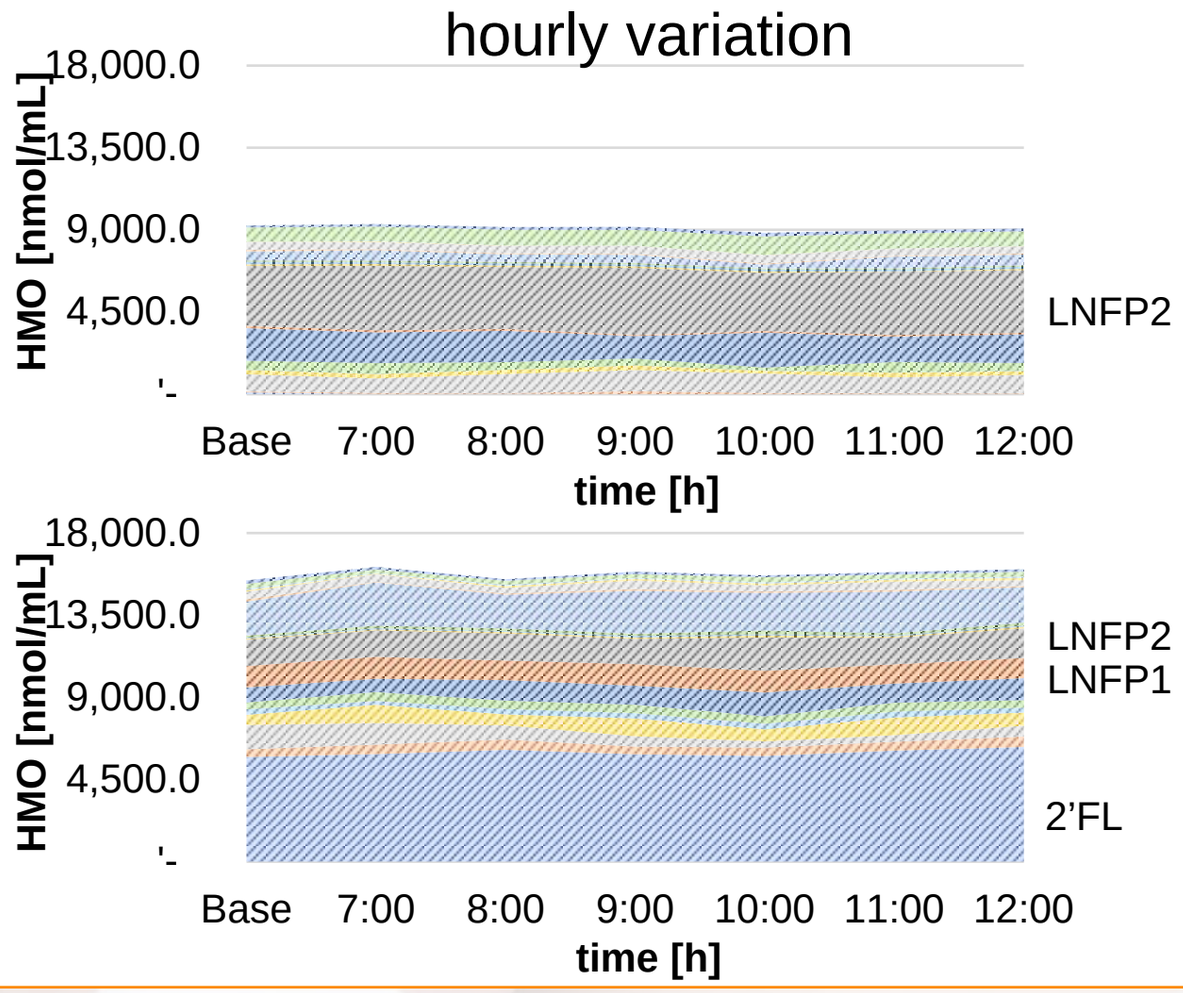
Azad, Bode et al. *J Nutrition* 2018

HMOs - MATERNAL DRIVERS

Interindividual variation







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manuscript in preparation

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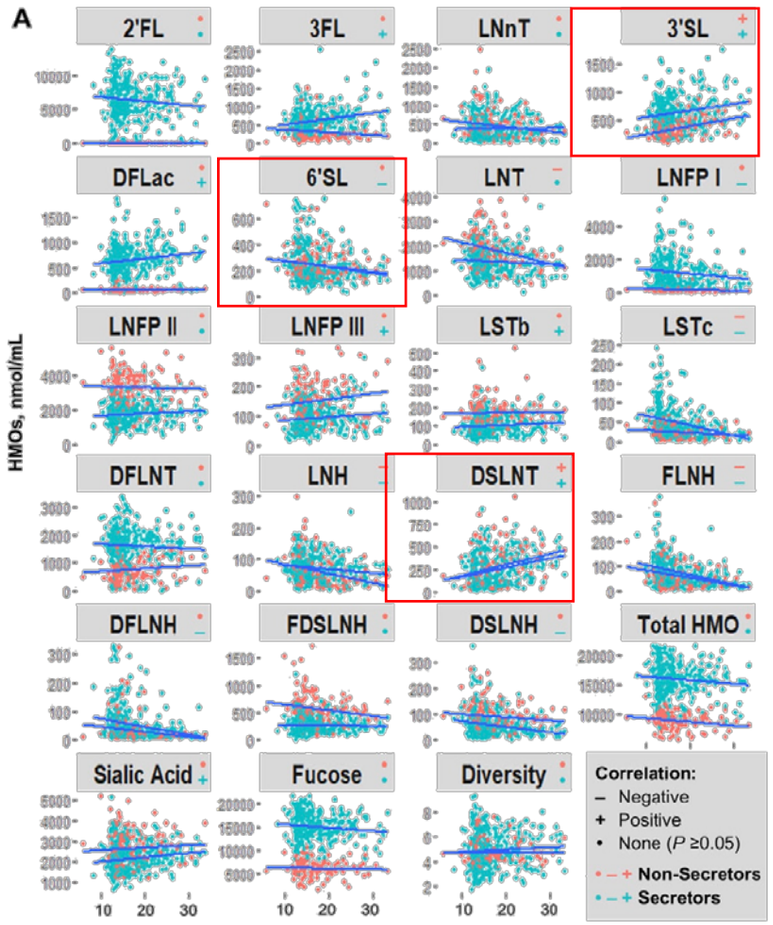
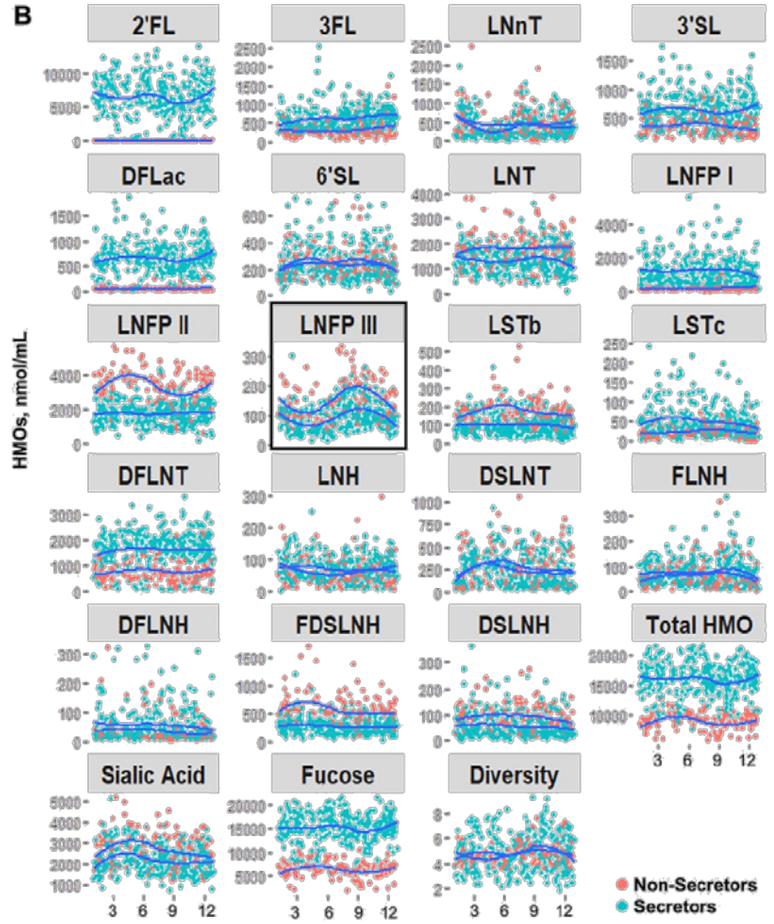
HMOs - MATERNAL DRIVERS
Dynamic over time





LRF MOMI CORE

Azad MB *et al. J Nutr* 2018;148:1–10

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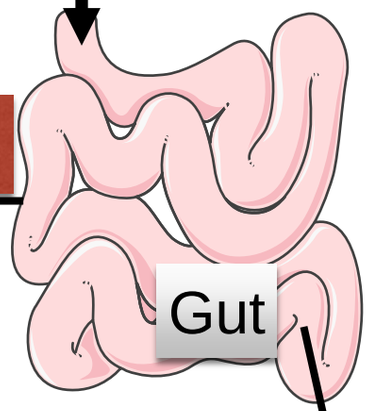
Differential Effects & Fate of Fructose vs Glucose (thinking beyond calories)

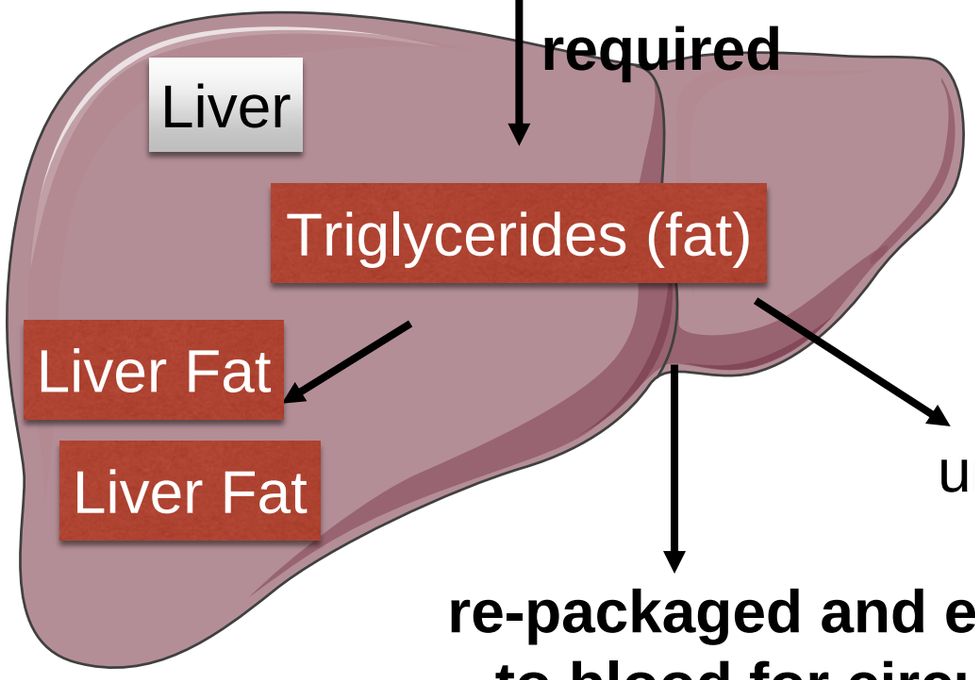
Fructose Fructose Glucose Glucose

Fructose Fructose



Fructose Fructose

“free entry”
No Insulin required



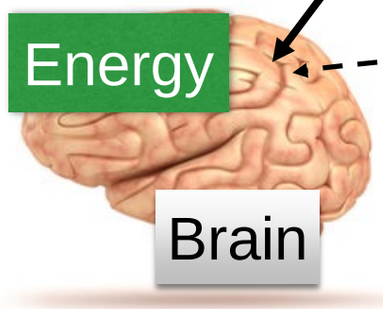
uric acid

re-packaged and exported to blood for circulation to other organs as VLDL-TG

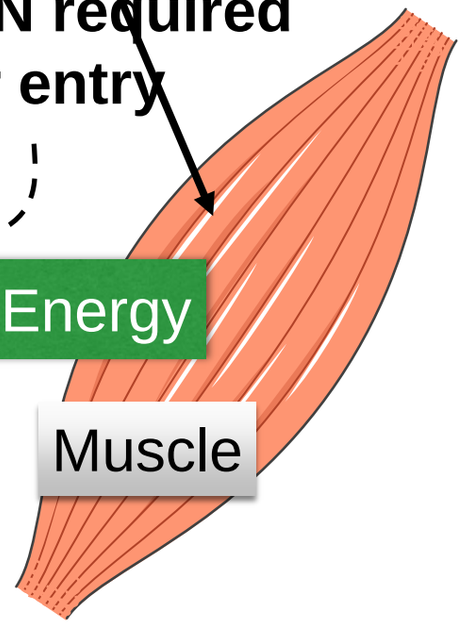
Glucose

INSULIN required for entry

Energy



Energy



$CO_2 + H_2O$

milk sugar (lactose)

Glucose — Galactose

Fructose

Fructose

GLUT-5 ✗

Fructose

fructose malabsorption

Fructose

“free entry” No Insulin required

Liver

Triglycerides (fat)

Liver Fat

Liver Fat

uric acid

re-packaged and exported to blood for circulation to other organs as VLDL-TG

Glucose

INSULIN required for entry

Galactose

Energy

Energy

$CO_2 + H_2O$

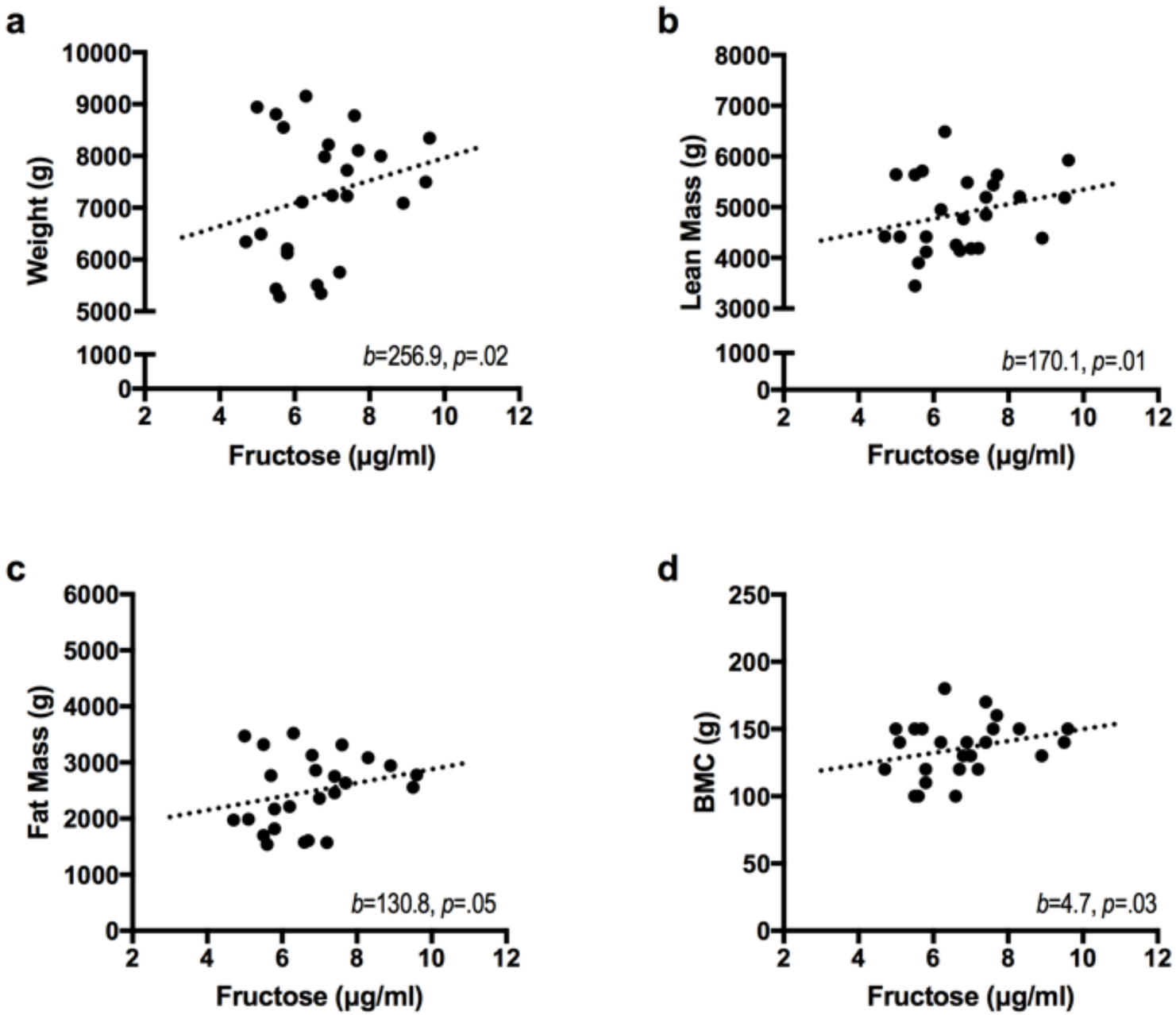
Pilot Study Data

- Pilot study One: 27 women who exclusively breastfed for 6 months; Caucasian women in Oklahoma City
- Breast milk samples at 1 and 6 months assayed for: a) common sugars (glucose, fructose, lactose); and b) the 17 most abundant HMOs
- Infant body fat measured at 1 and 6 months by DEXA

- Pilot study Two: Acute effects of sugar ingestion on changes in breastmilk sugars and breastmilk HMOs over 6h

- Collaboration with Lars Bode (UCSD) and David Fields (OHSU)

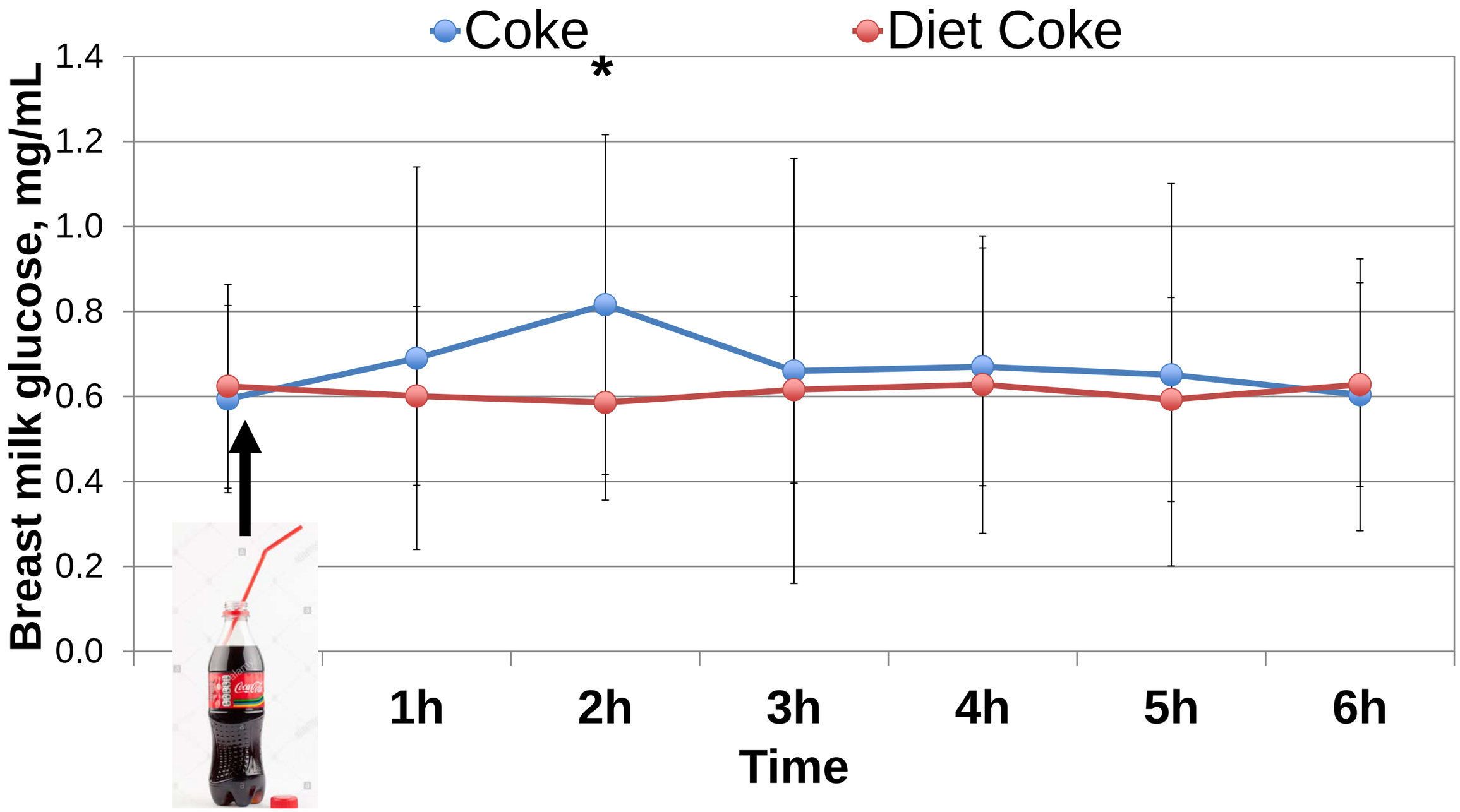
Fructose: Present in Low Concentrations in Breast Milk and Associated With Infant Body Composition



Goran et al, Nutrients 2017

independent of maternal BMI; no relationships with other breast milk sugars

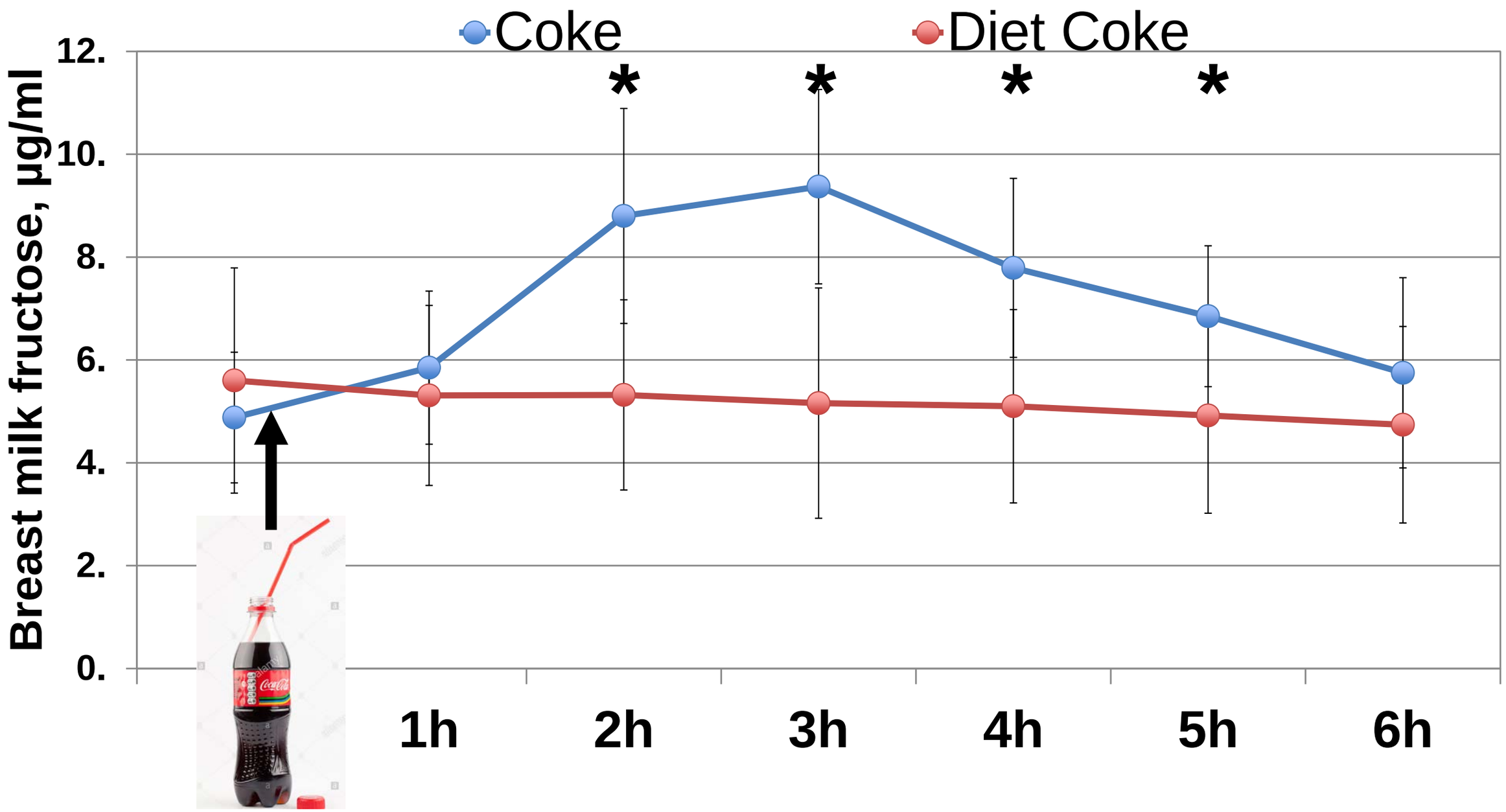
Minimal Transfer of Glucose Into Breastmilk After Maternal Consumption of a Glucose and Fructose Mixture



No significant Coke effect (P=0.42); No significant time effect (P=0.64);
No significant Coke x time interaction (P=0.19)

Berger et al, 2018

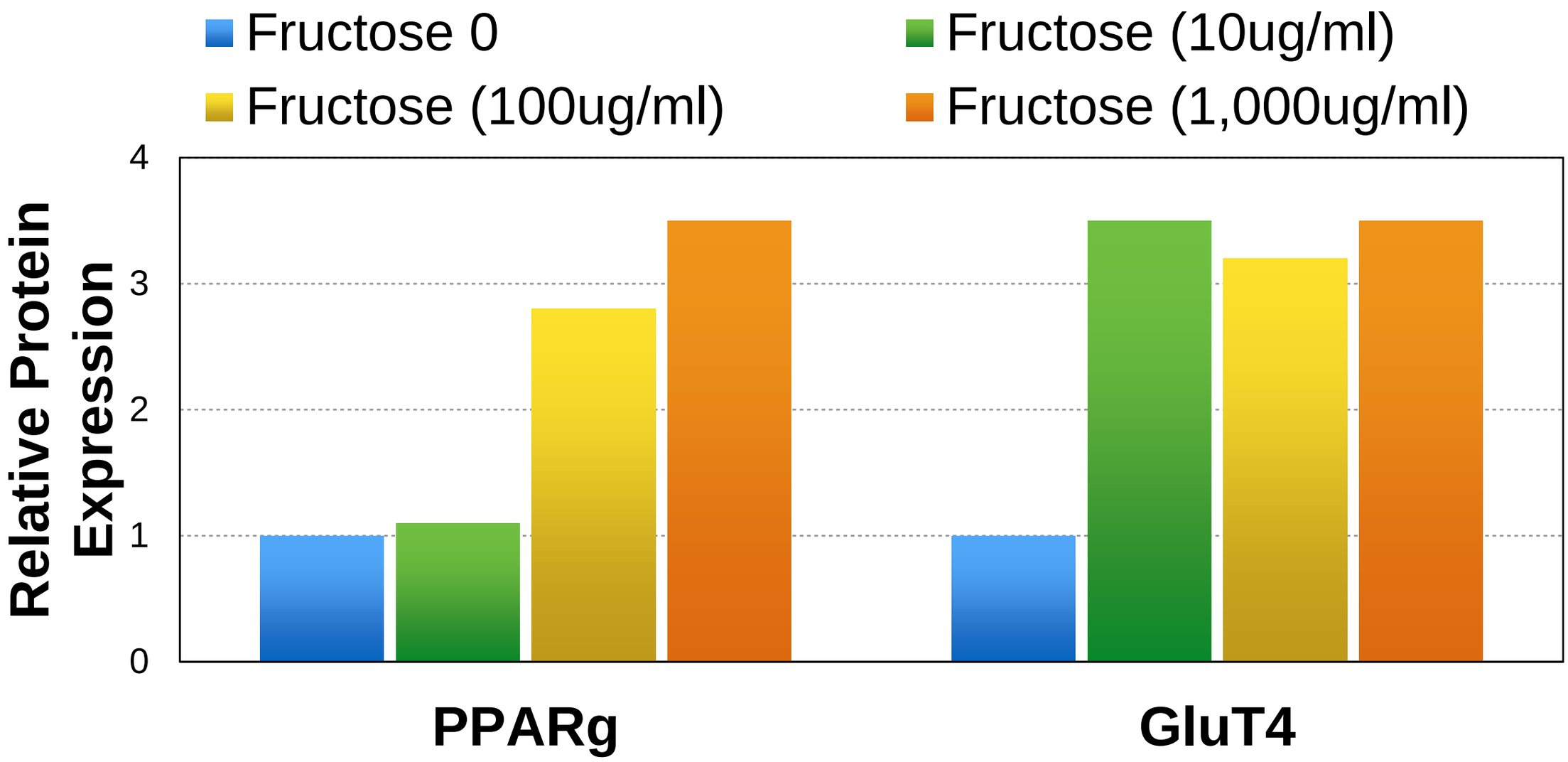
Significant and Sustained Transfer of Fructose Into Breastmilk After Maternal Consumption of a Glucose and Fructose Mixture



Significant Coke effect (P<0.01); Significant time effect (P<0.01);
Significant Coke x time interaction (P<0.01)
Effect sustained for 5h post consumption

Berger et al, 2018

Pre-Adipocytes: Very Sensitive to Low Levels of Fructose at Concentrations Found in Breast Milk



In transgenic mice over expressing Glut4 in adipose tissue:
improved glucose tolerance BUT
2-3 fold increase in total body fat through adipocyte hyperplasia
(Shepherd et al 1993)

Du & Heaney, Mol Endocrinology, 2012

Mothers Milk Study

Recruiting 240 Hispanic women/newborns

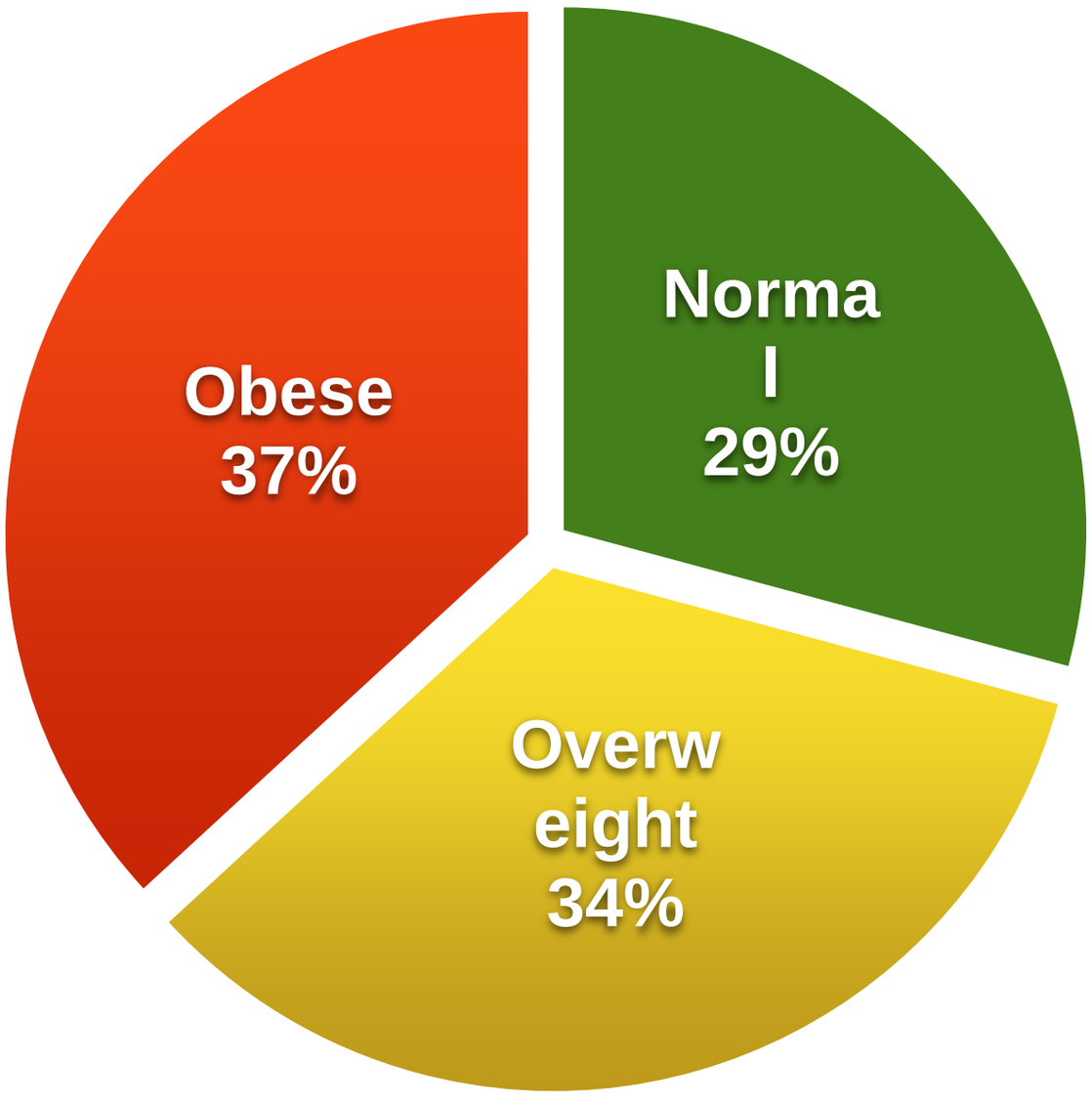
Collect mother's milk and infant stool
maternal and infant diet and obesity
measures every 6 months over 2 years

Identify maternal dietary factors and/or
compounds in mothers milk that:

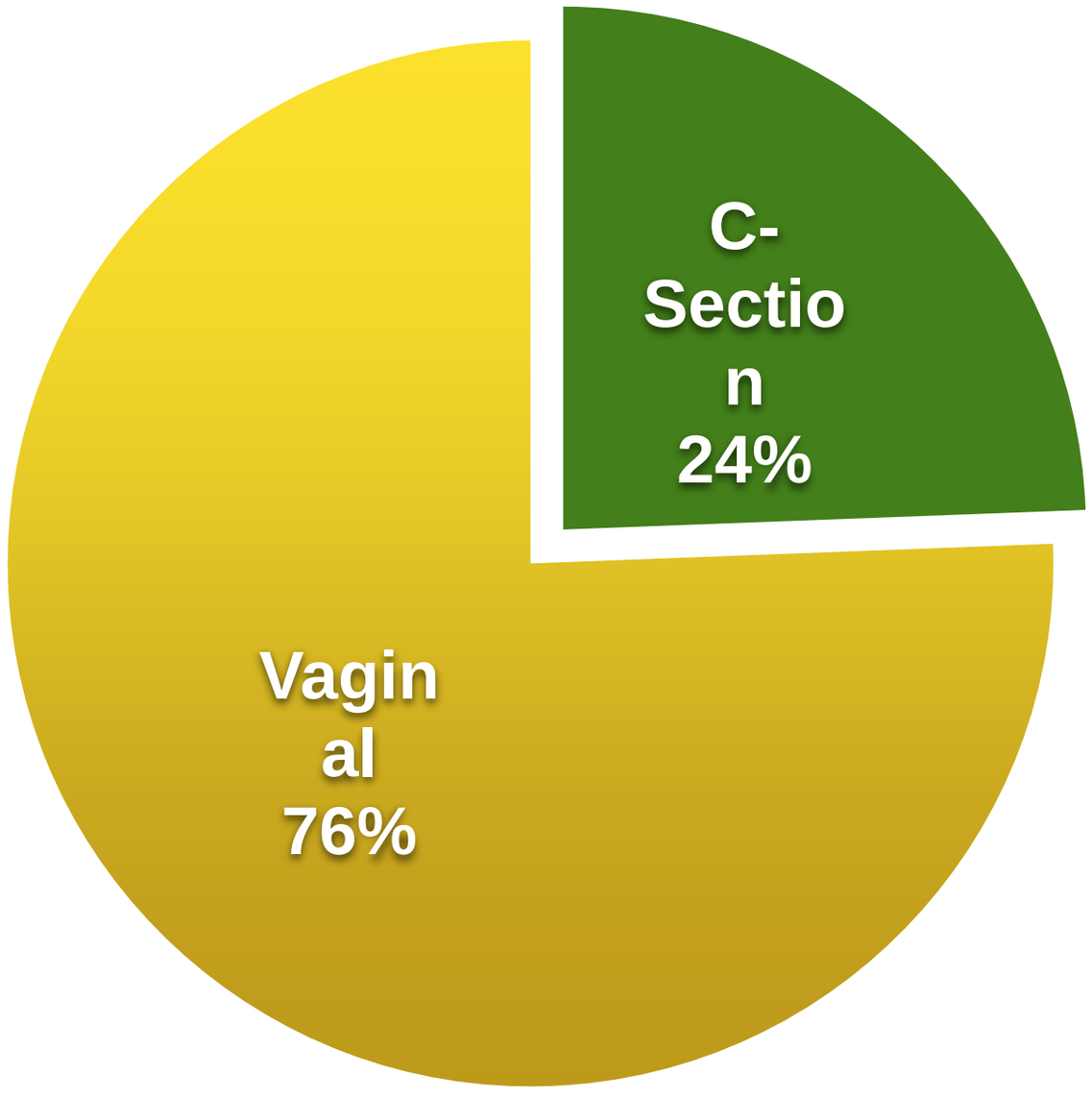
establish healthy gut bacteria
Prevent obesity
Promote cognitive development

Funded by Gerber Foundation and RO1 from NIDDK

Weight Status of Mothers (pre-pregnancy BMI)



Birth Mode

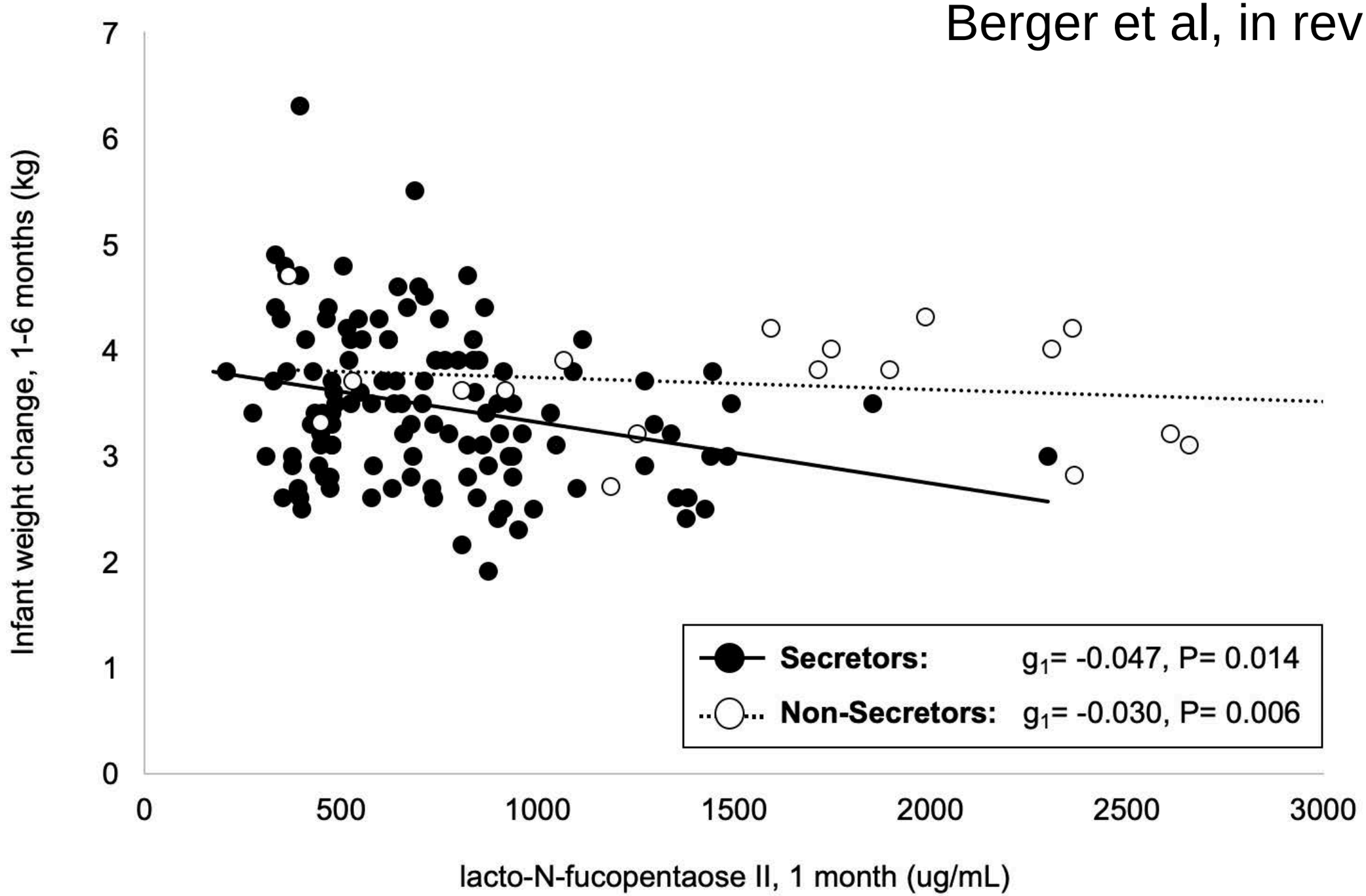


Relationship Between HMOs at 1-month and Infant Weight Gain in First 6-Months

	Total	Secretor	Non-secretor	P
n	157	135	22	
Mothers				
Age at delivery (years)	28.7 ± 6.1	28.7 ± 6.2	28.8 ± 5.5	0.94
BMI, pre-pregnancy (kg/m^2)	28.2 ± 5.7	28.2 ± 5.8	28.0 ± 4.9	0.89
Caesarean delivery (%)[d]	25.6	25.4	27.3	0.85
Infants				
Female (%)[d]	53.2	52.2	59.1	0.55
Age (days)	32.5 ± 4.5	32.6 ± 4.6	32.5 ± 4.1	0.93
Birth weight (kg)	3.39 ± 0.4	3.40 ± 0.4	3.33 ± 0.5	0.48
Weight, 1 month (kg)	4.59 ± 0.5	4.59 ± 0.5	4.58 ± 0.6	0.89
Weight, 6 months (kg)	8.02 ± 0.8	8.02 ± 0.8	8.11 ± 0.8	0.68
Change in weight, 1-6 months (kg)	3.44 ± 0.7	3.41 ± 0.7	3.62 ± 0.5	0.26
WAZ, 1 month	0.42 ± 0.8	0.42 ± 0.8	0.41 ± 0.9	0.98
WAZ, 6 months	0.44 ± 0.8	0.42 ± 0.8	0.56 ± 0.8	0.51
Change in WAZ, 1-6 months	0.02 ± 0.8	-0.02 ± 0.8	0.30 ± 0.7	0.15

Higher LNFPII at 1-Month Associated With Lower Weight Gain Over 6 Months

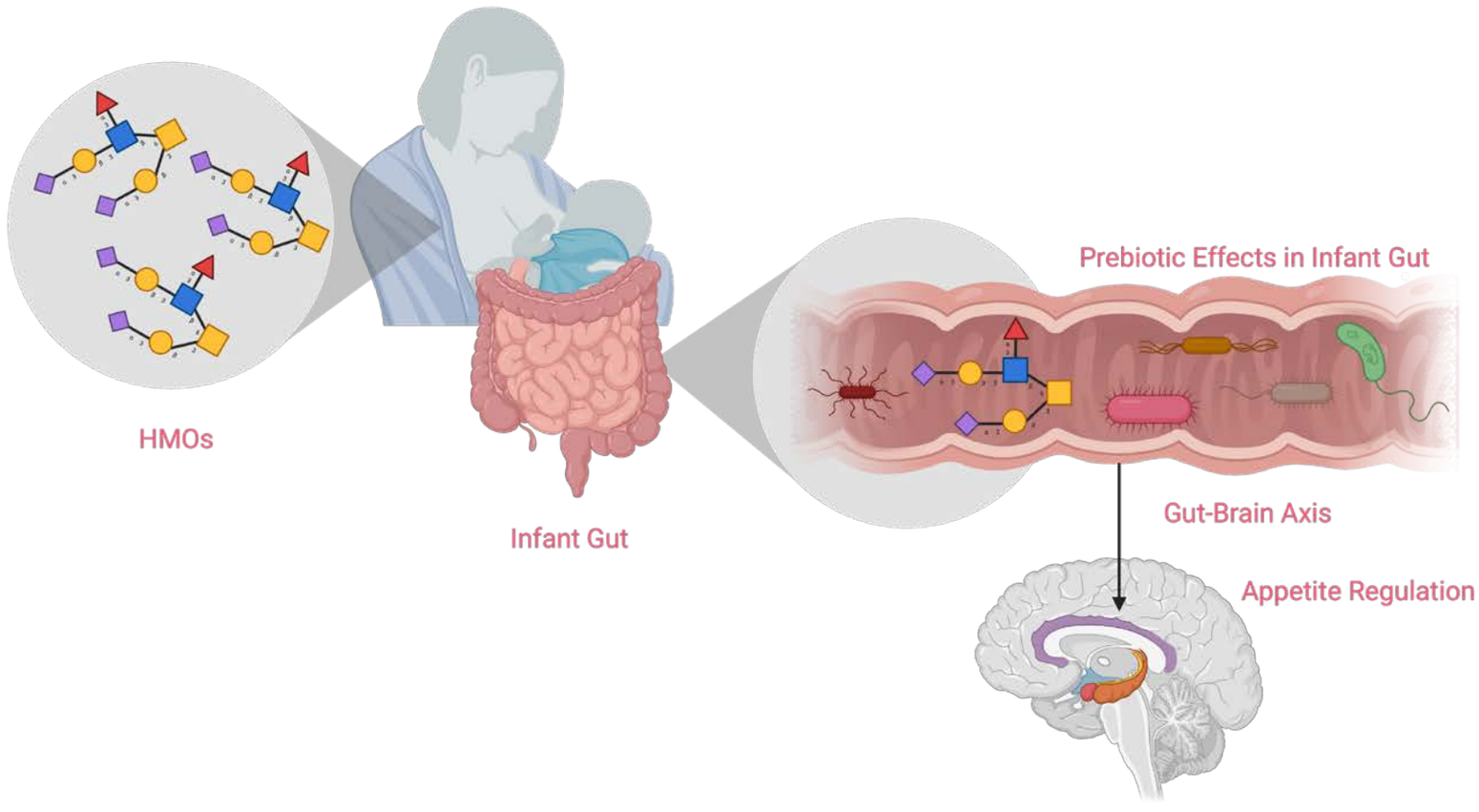
Berger et al, in revision



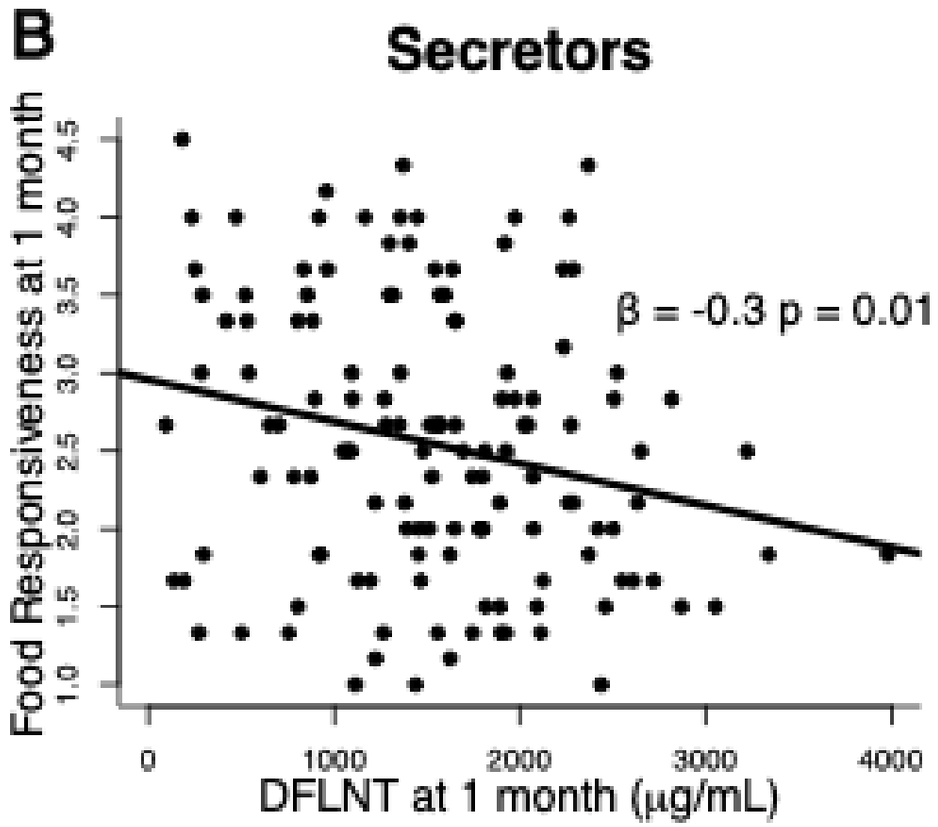
Adjusted for maternal age, pre-pregnancy BMI, infant age, sex, and birth weight.
Similar findings were observed for WAZ gain.

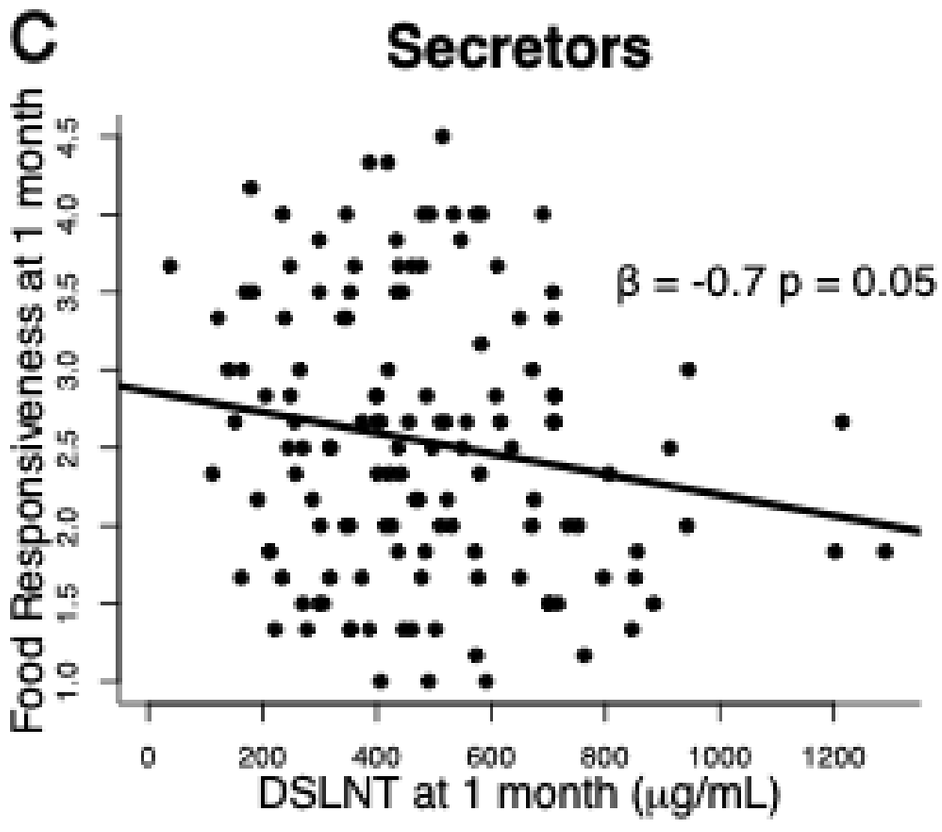
HMOs and Infant Feeding Behavior

- Mother-infant feeding behaviors assessed with Baby Behavioral Eating Questionnaire (BBQ)
- Measures several domains including “food responsiveness” which is urge to eat when see, taste or smell palatable food
- In some studies food responsiveness in infancy predicts greater infant weight gain



Plows et al, in review





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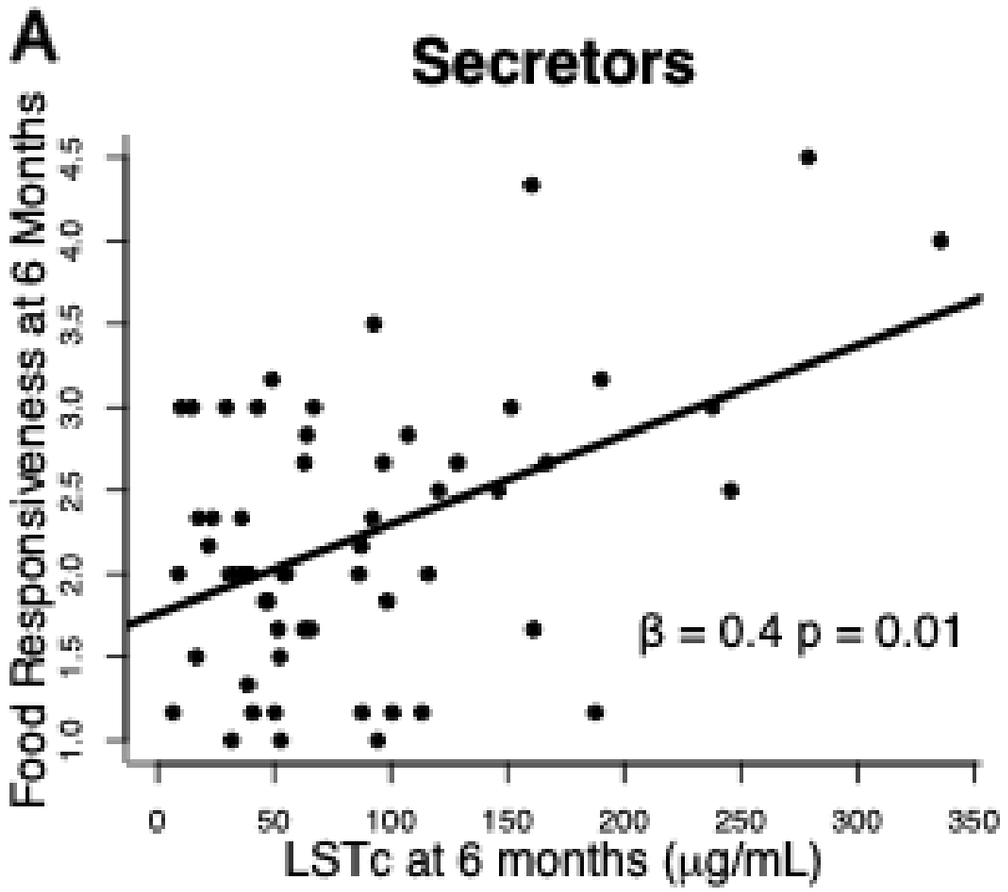
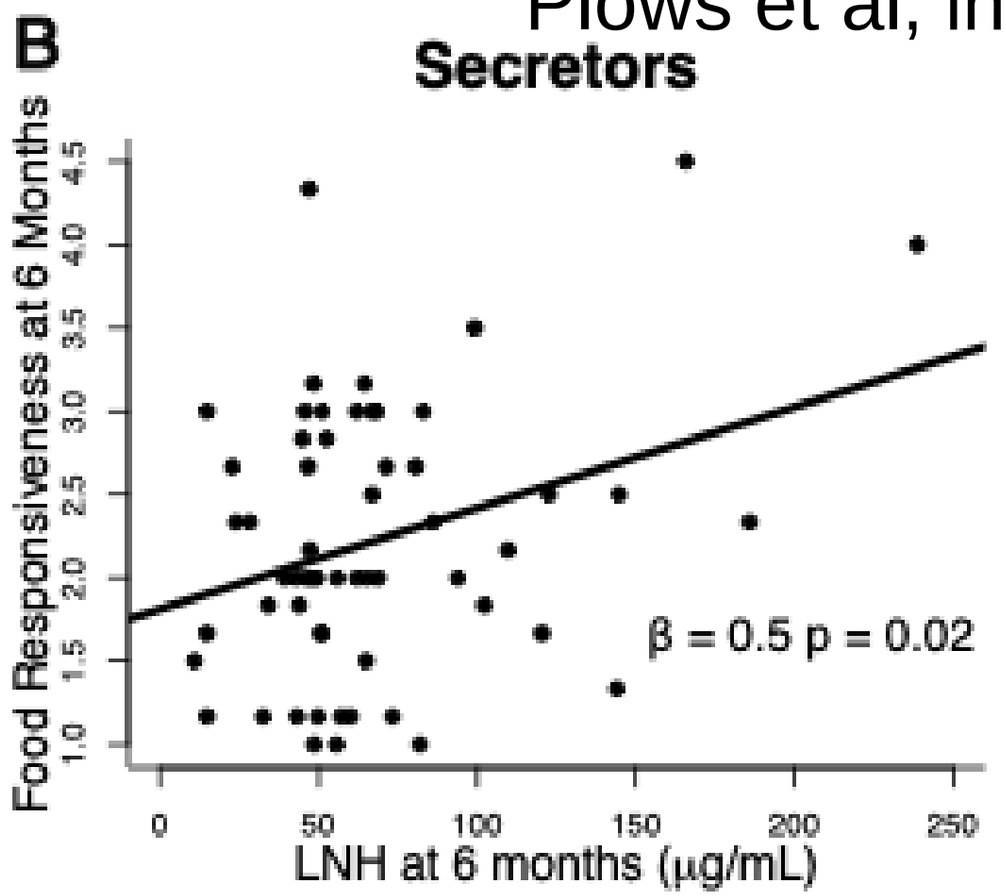
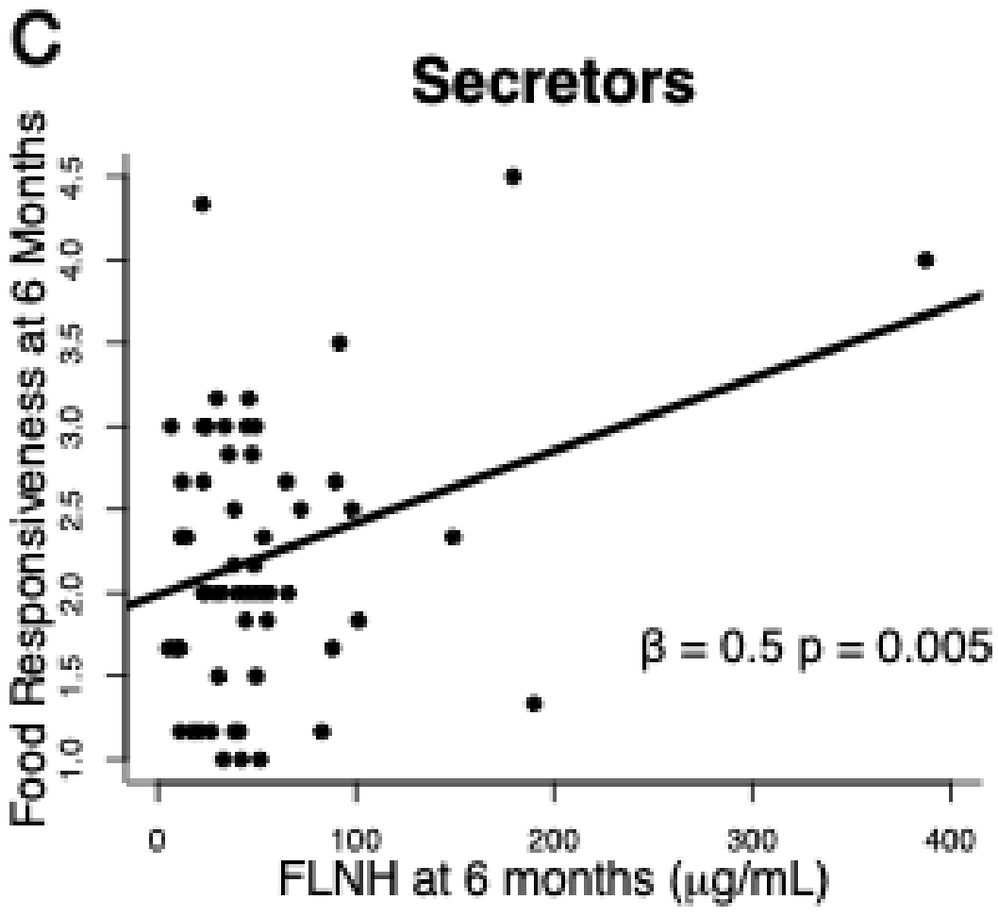
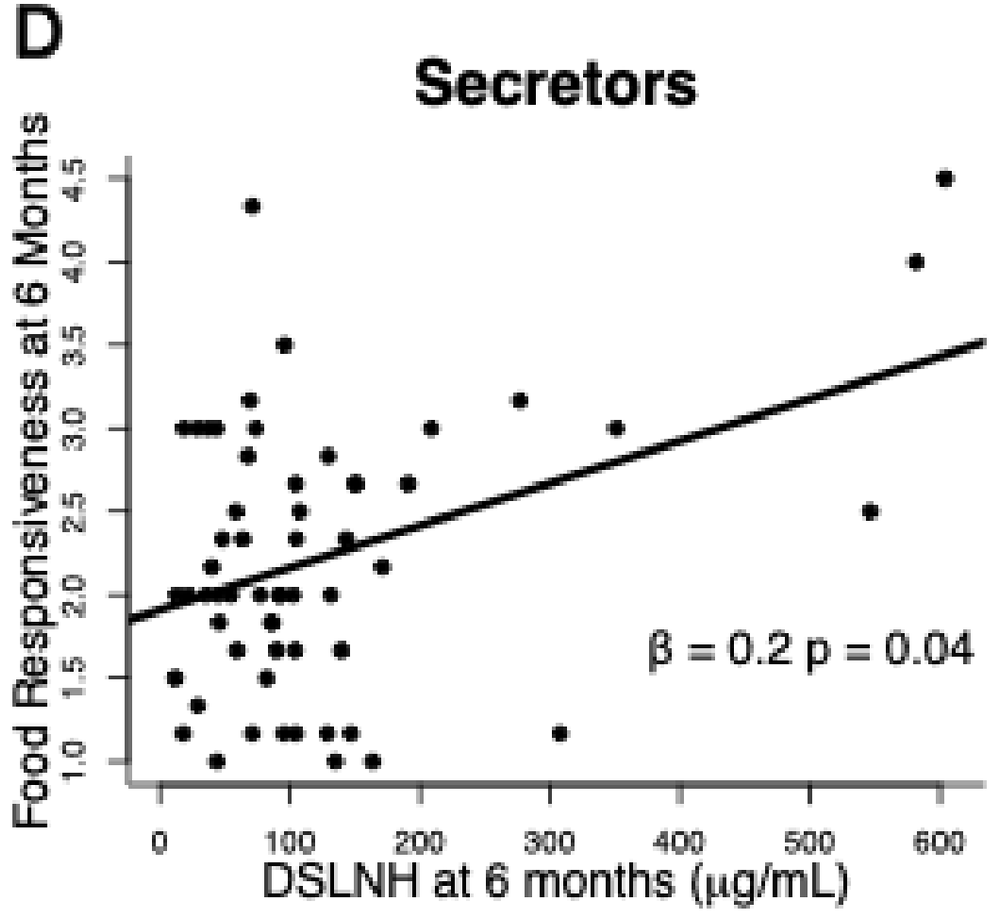








Summary: HMOs and Infant Food Responsiveness

HMO	Timepoint	Food Responsiveness/Appetite
Sum	1 month	Decreased
DFLNT	1 month	Decreased
DSLNT	1 month	Decreased
FLNH	6 months	Increased
LSTc	6 months	Increased
LNH	6 months	Increased
DSLNH	6 months	Increased

Role of 2'FL in Infant Cognitive Development

- Animal studies show 2'FL enhances learning, memory and attention in rodents
- Used as a supplement in some infant formula
- No human studies
- Examined links between HMOs at 1-month and 6-month and measures of infant cognitive development at 24-months using the Bailey's test

Bayley-III Scales:
Infant and Toddler Development

Cognitive

Language

Motor

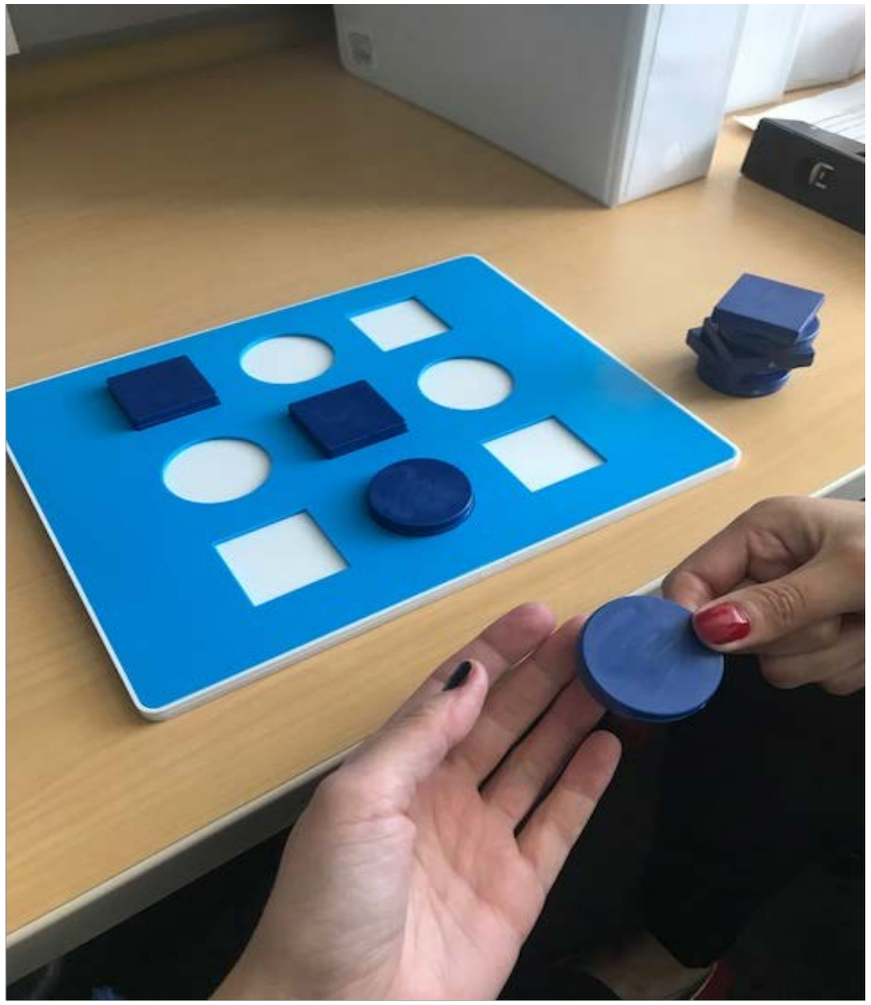
Includes assessment of the following skills :

- Sensorimotor integration
  - Attention
    - Memory
  - Habituation
- Concept formation

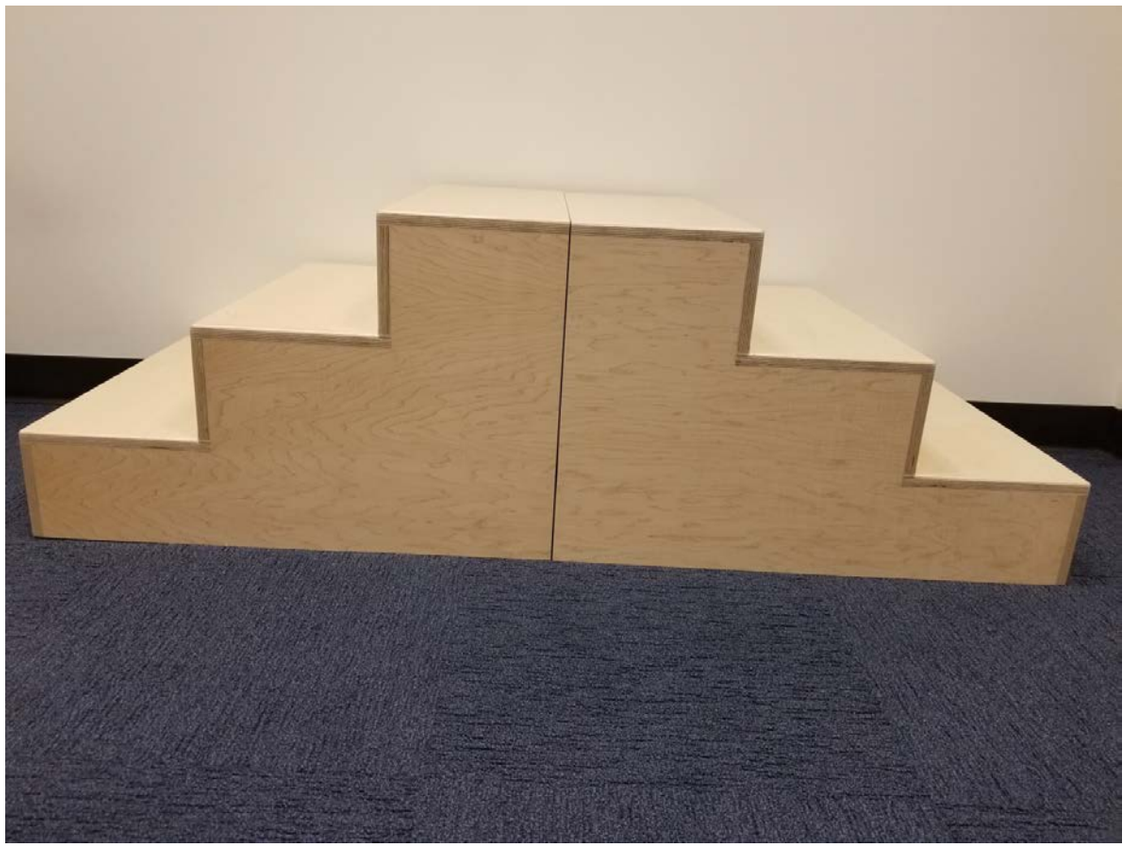
- Receptive
- Expressive

- Gross
- Fine

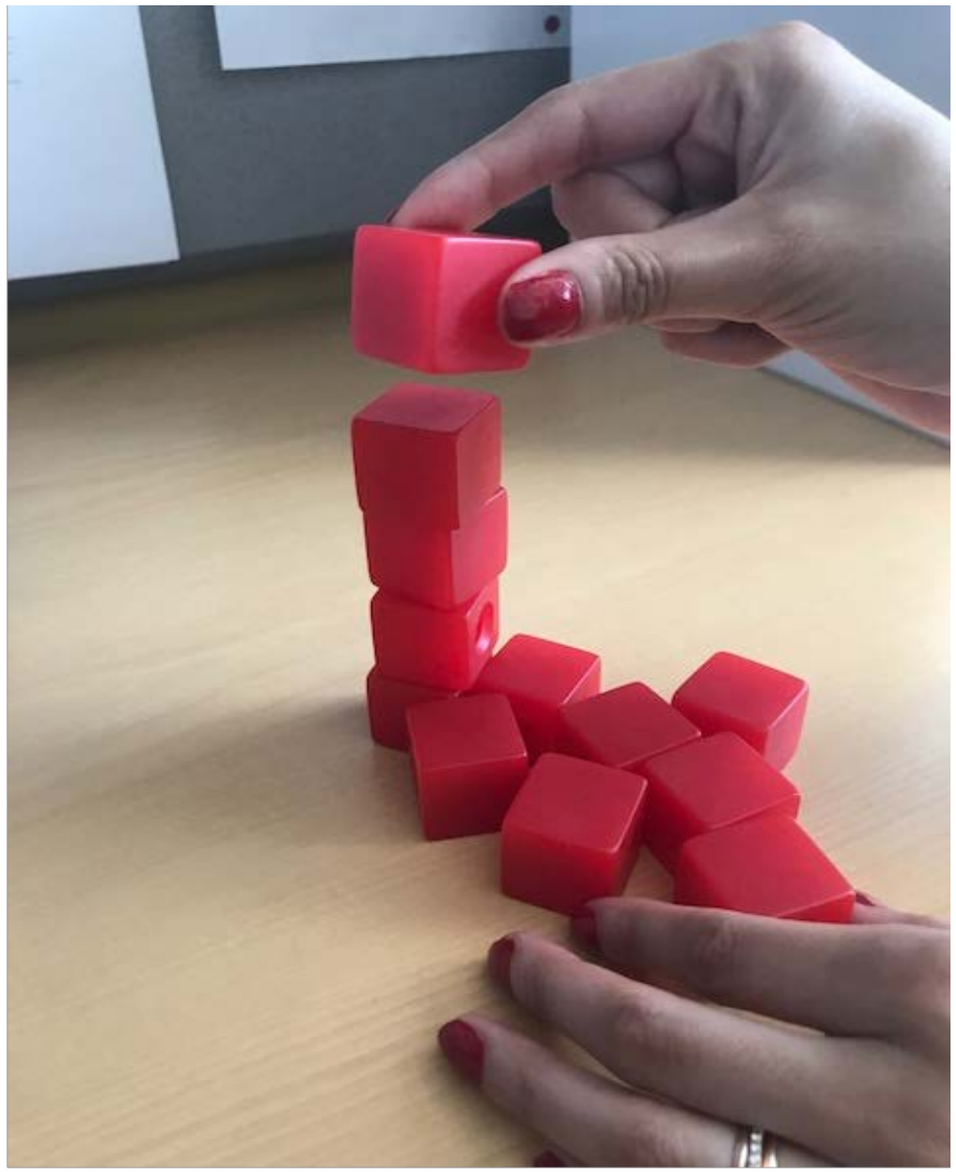
Cognitive Tests



Gross Motor

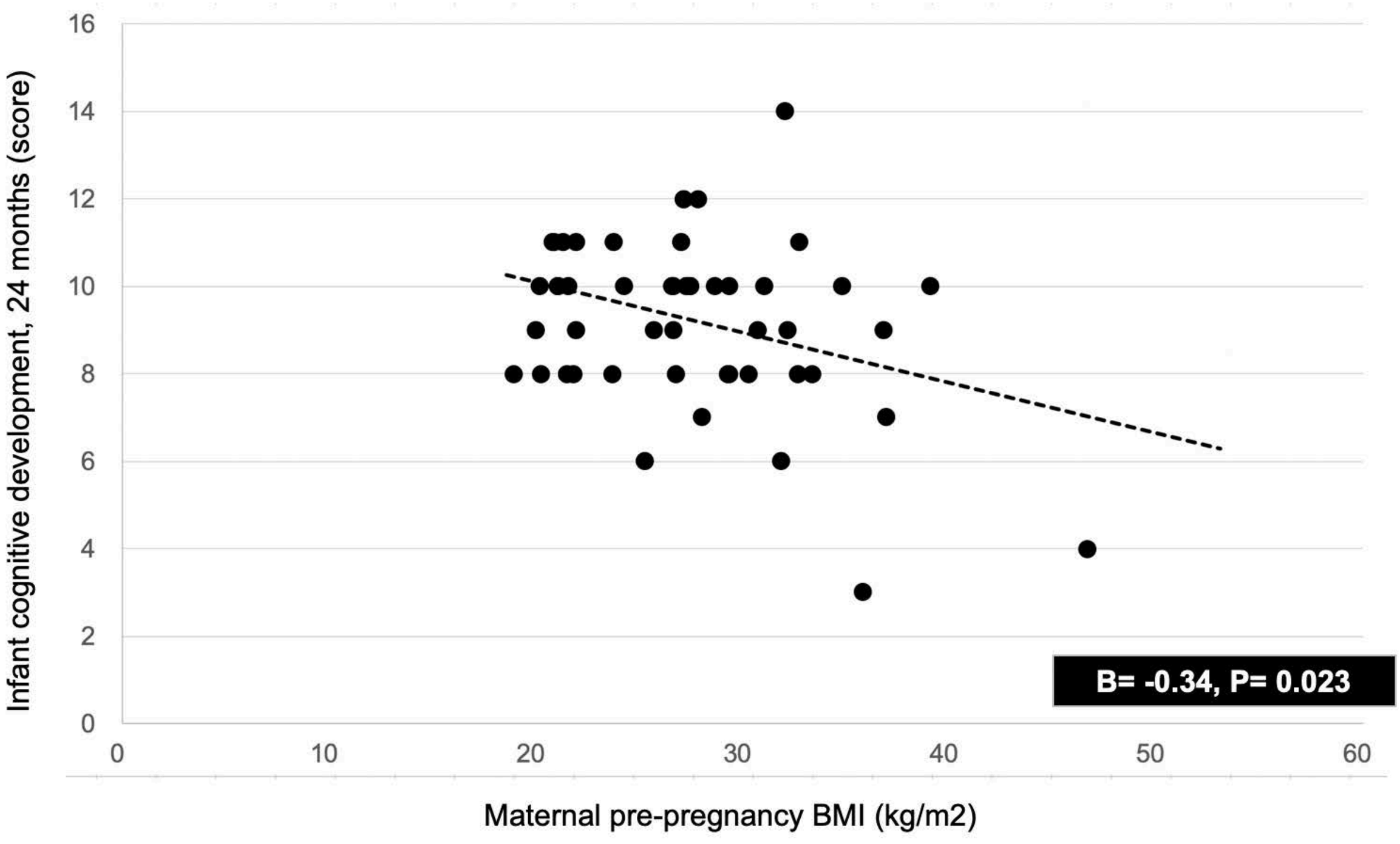


Fine Motor



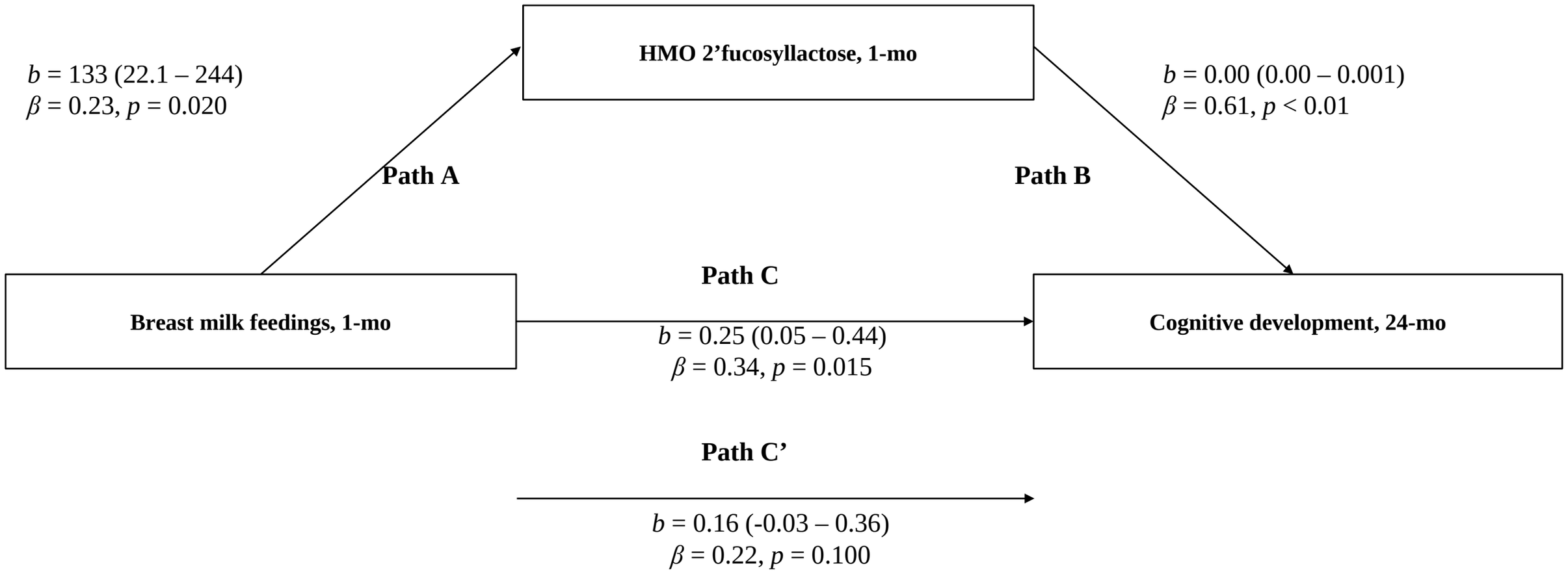
Pre-Pregnancy BMI Associated With Lower Infant Cognitive Development Score

Berger et al, PLOS One, 2020



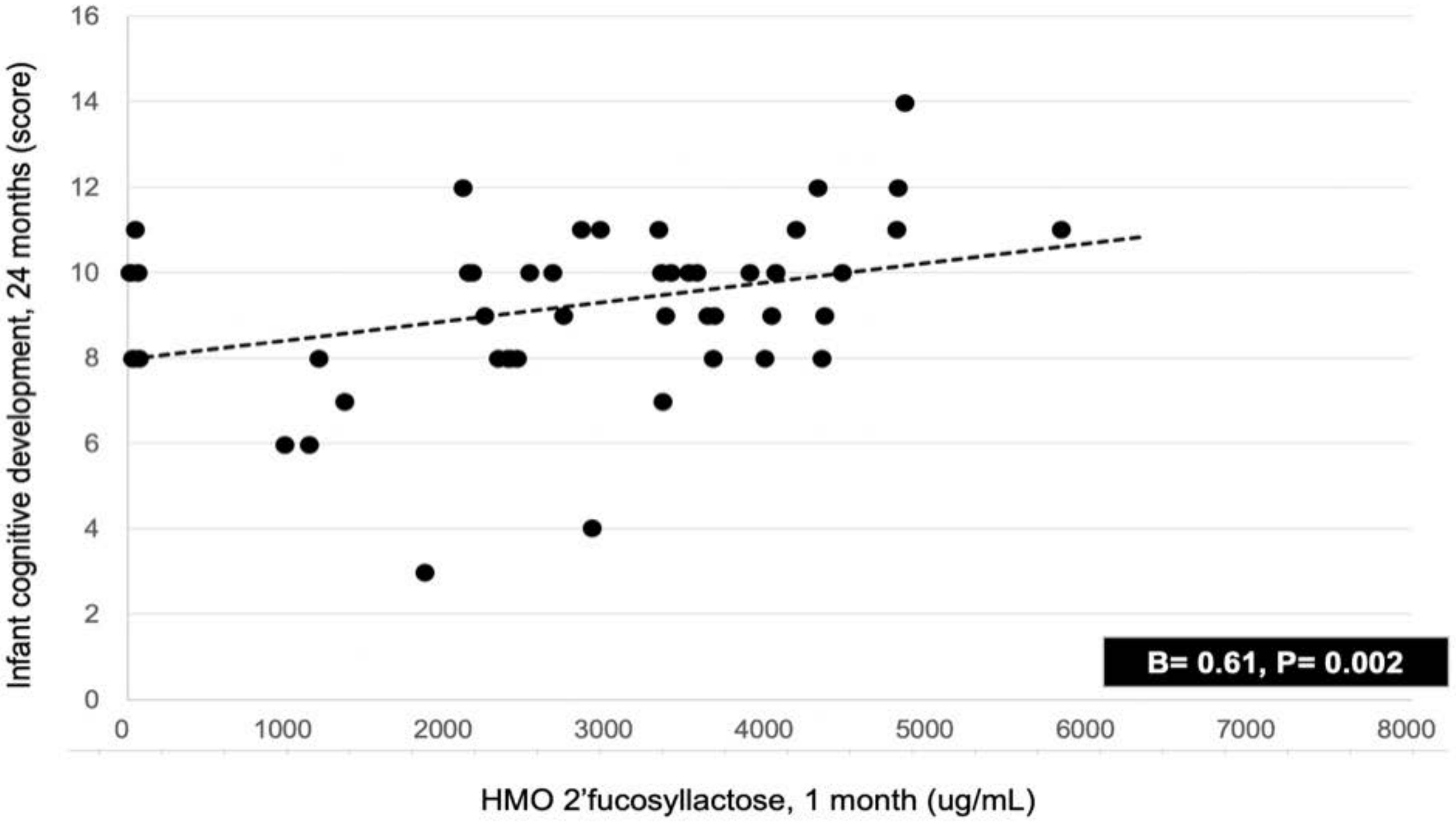
2'FL Mediates the Relationship Between Number of Breast Milk Feedings and Cognitive Development at 24-months

Berger et al, PLOS One, 2020



2’Fucosyllactose at 1 Month (but not 6 Months) Associated With Higher Infant Cognitive Development at 24-Months

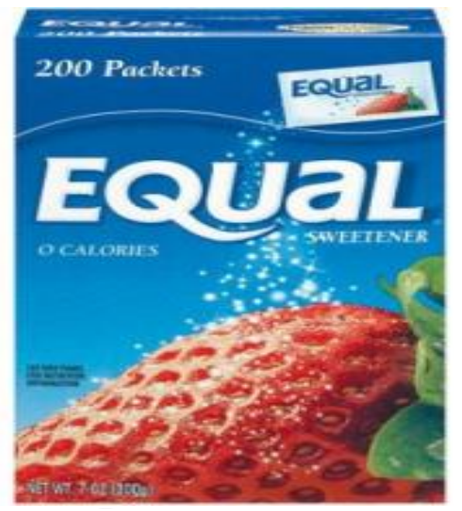
Berger et al, PLOS One, 2020



Low Calorie Sweeteners (LCS)

SUCRALOSE
600 times sweeter
Not absorbed

SACCHARIN
200-700 times sweeter
excreted in urine



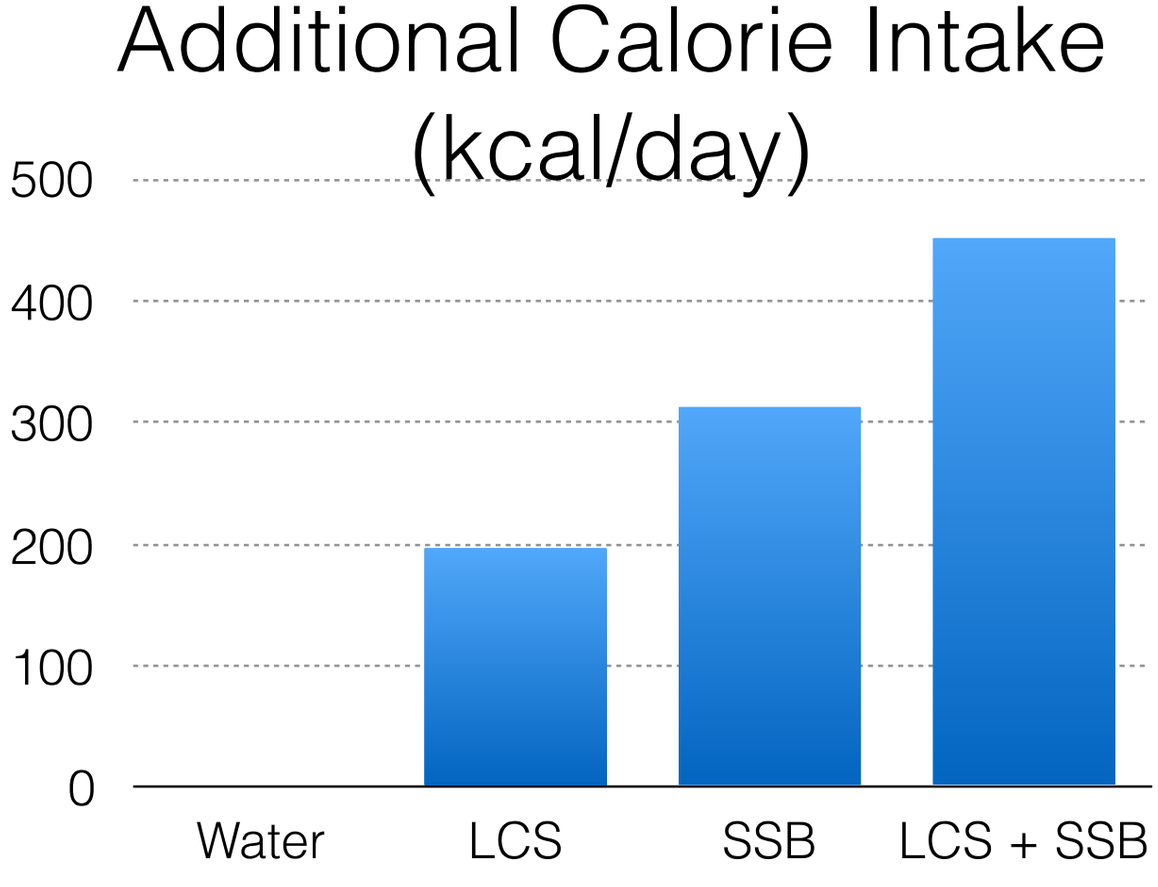
ASPARTAME
200 times sweeter
broken down to Phe, AspAcid & Methanol

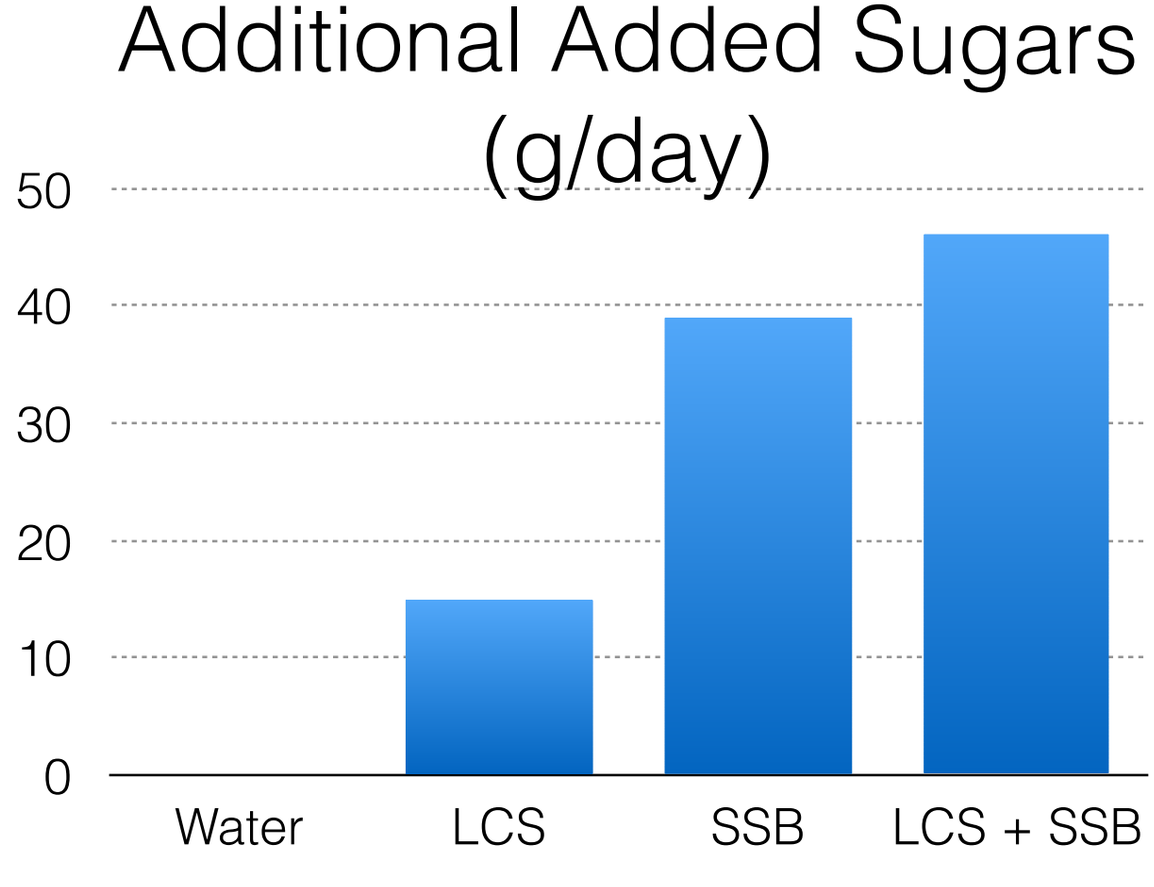
REBAUDIOSIDE A (STEVIA)
200-300 times sweeter
Not absorbed

ACESULFAME-K
200 times sweeter
excreted in urine

Do LCS Consumers Consume Less Calories or Less Sugar? NO

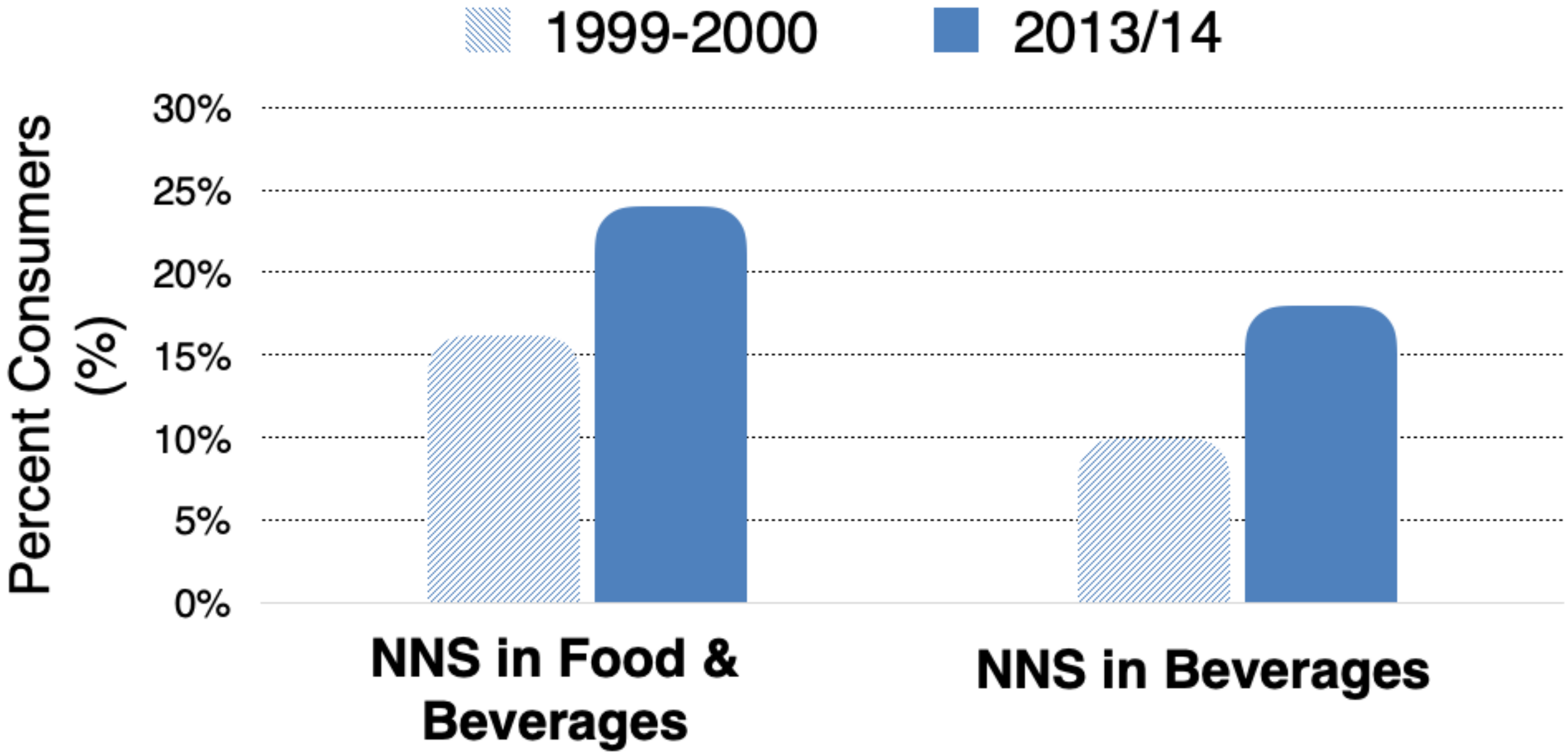
Data from 7,026 children from NHANES 2011-2016; Separated into 3 groups consuming predominantly:
Water
LCS beverages,
sugary beverages
LCS + sugary beverages





Slyvetsky et al; Ped Obesity 2019

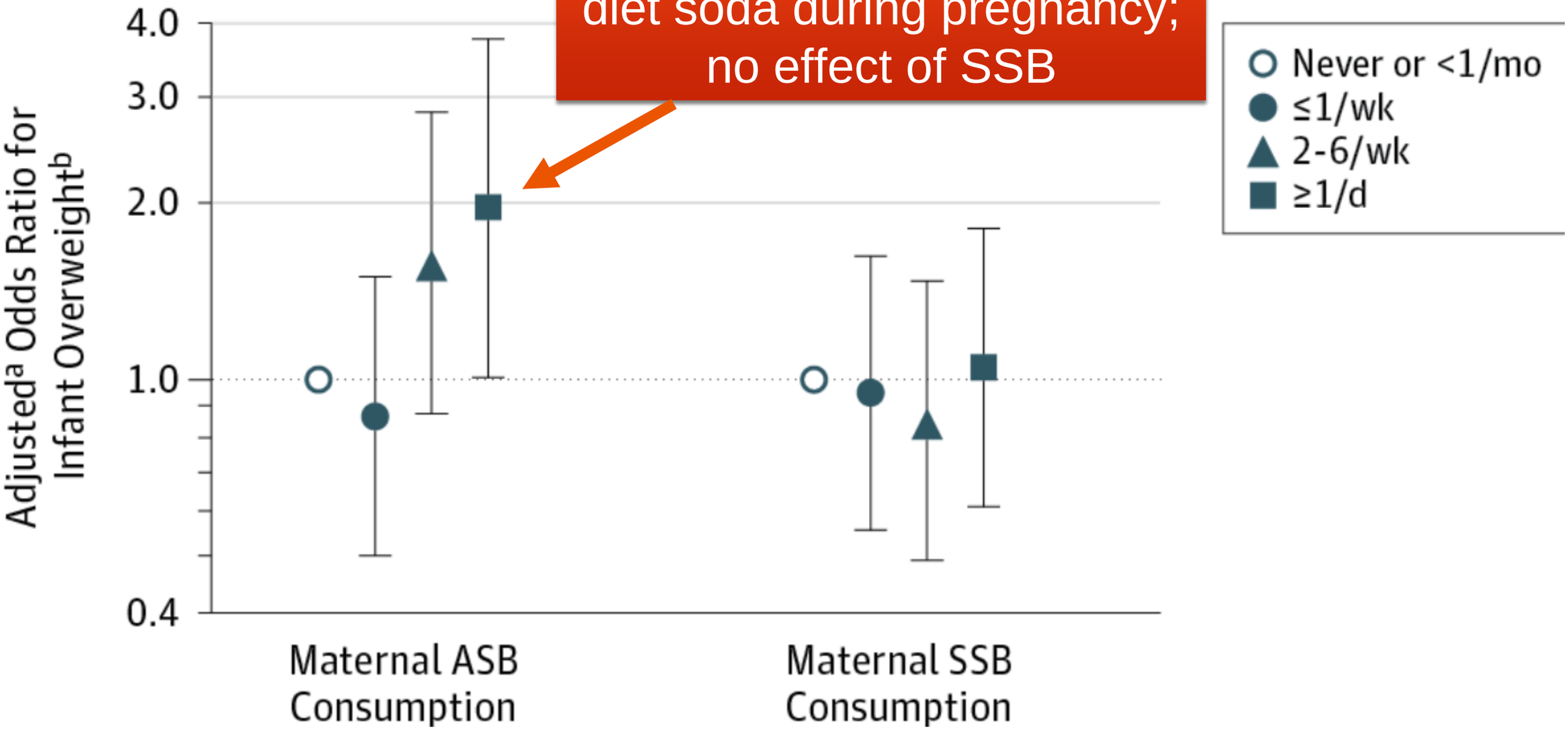
Increase in NNS Consumption in Pregnant Women in the US (NHANES data)



Sylvetsky et al. 2019

Association Between Diet (LCS) Beverage Consumption During Pregnancy and Infant Body Mass Index

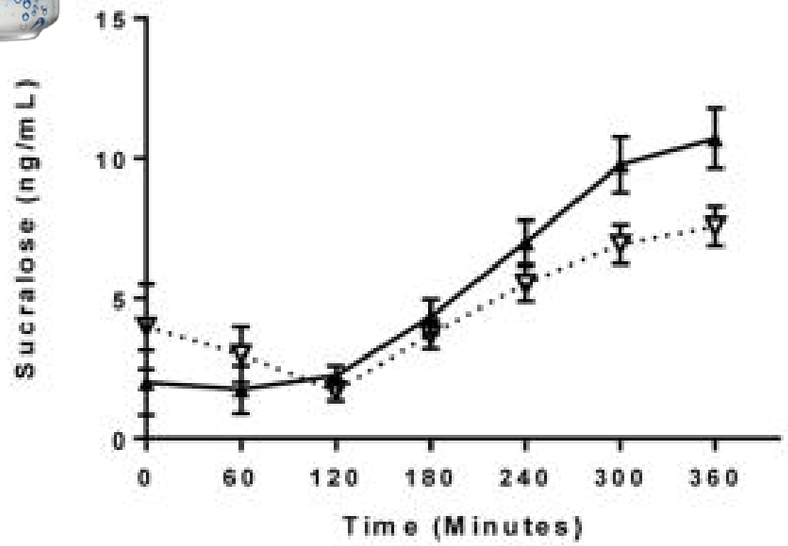
2 fold increase in risk of infant overweight after daily diet soda during pregnancy; no effect of SSB



JAMA Pediatr. 2016;170(7):662-670. doi:10.1001/jamapediatrics.2016.0301; Azad et al

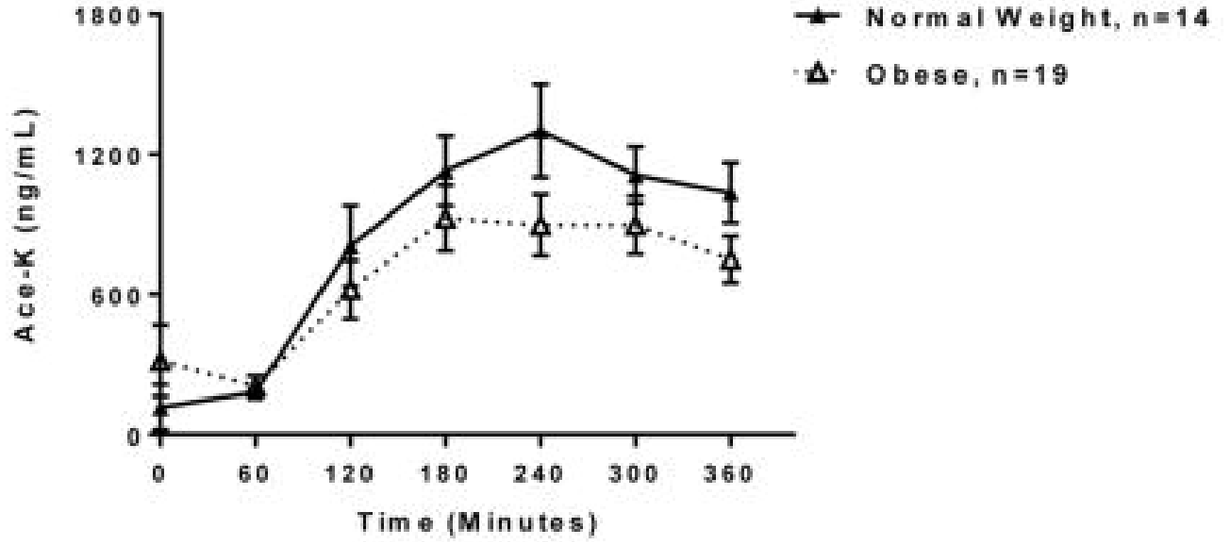
Significant and Sustained Transfer of Non-Nutritive Sweeteners in Breastmilk

Sucralose



Sucralose concentrations were higher in normal weight women, but not when adjusted for blood volume

Ace-k



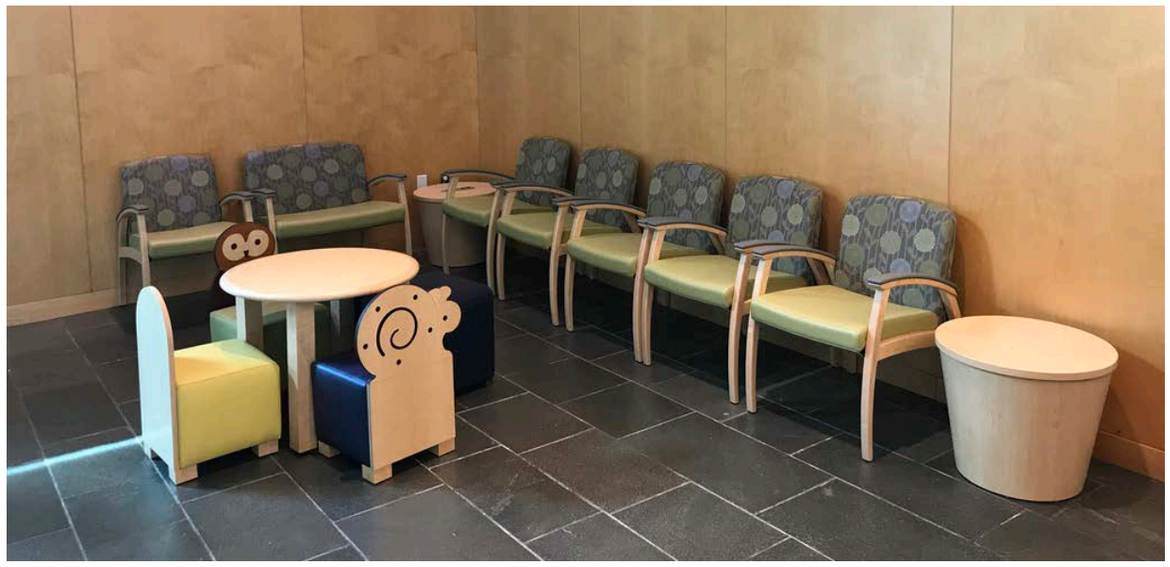
No difference in ace-k concentrations between normal weight and obese women

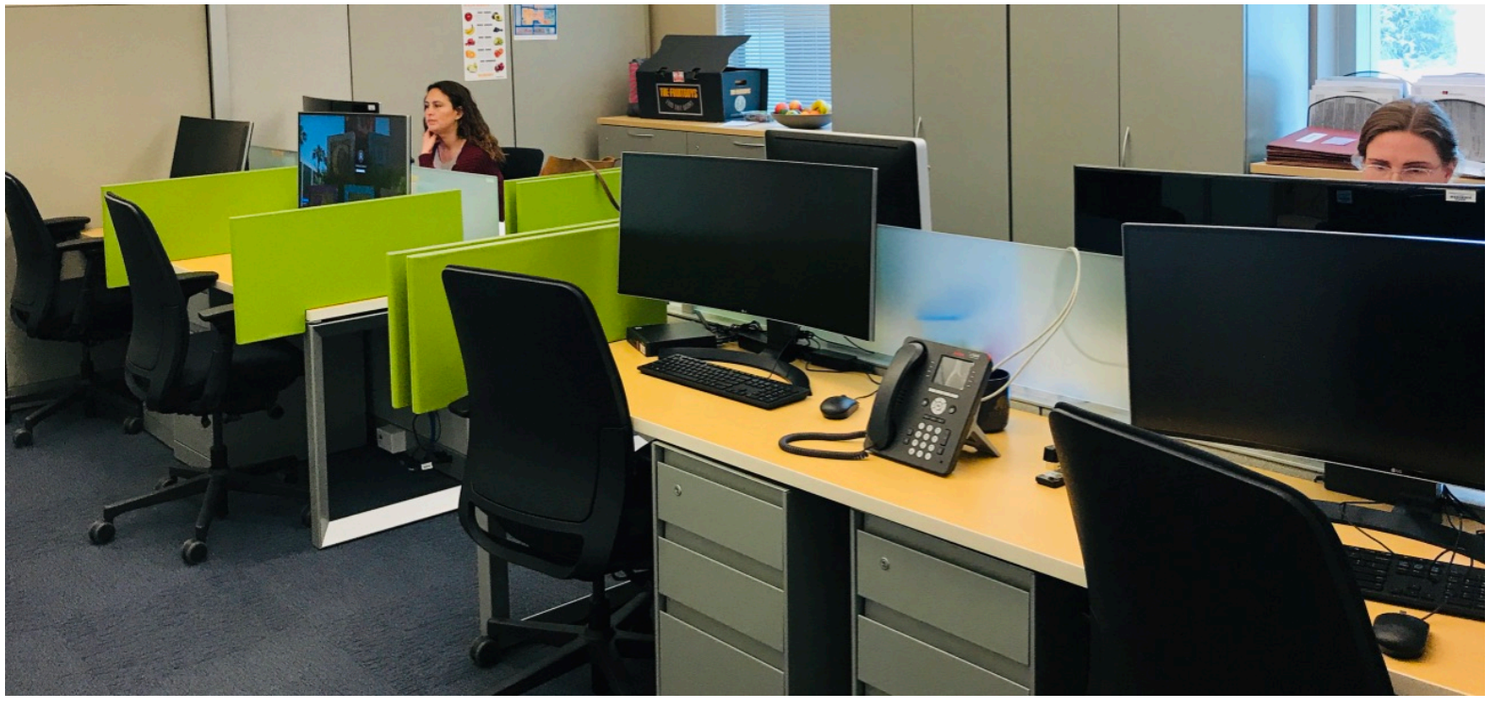
Rother et al. 2018

The Amazingly Dedicated People Who Get the Studies Done

Briannie Orellana, Carla Flores, Claudia Rios, Danielle Garcia, Elizabeth Campbell

Emily Leibovitch, Margarita Guiterrez, Marisol Reveles, Paola Garcia, Rosa Rangel, Rosalba Cain, Synthia Arcadia, Yessica Coran,





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