


Obesity, Milk, and Offspring Outcomes.
Lactation Insights from a Mouse Model and Clinical Data

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- No conflicts of interest to disclose

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Outline

- Introduction
- Mouse Model of Obesity during Lactation and Offspring Outcomes
- Exploratory Analysis of the Association Between Breast Milk Lipids and Infant Adiposity
- Conclusion

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Introduction

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Developmental Origins of Health and Disease (DOHaD) Theory


- Emerged from epidemiological studies looking at infant and adult health
- Early life exposures are associated with adult health outcomes



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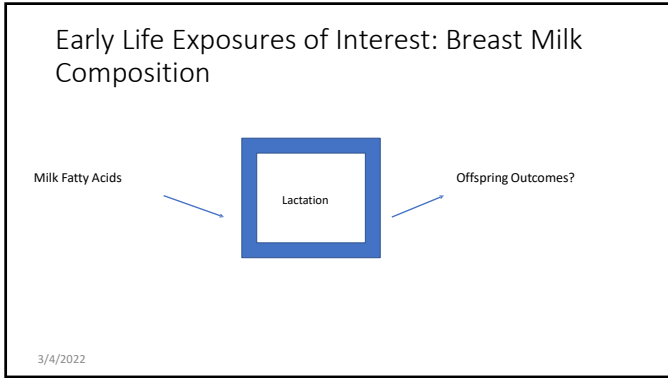
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Early Life Exposures of Interest: Obesity



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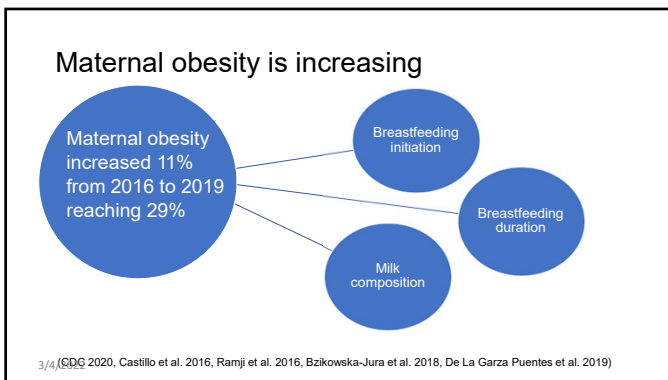


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Activation of Adipocyte mTORC1 Increases Milk Lipids in a Mouse Model of Lactation

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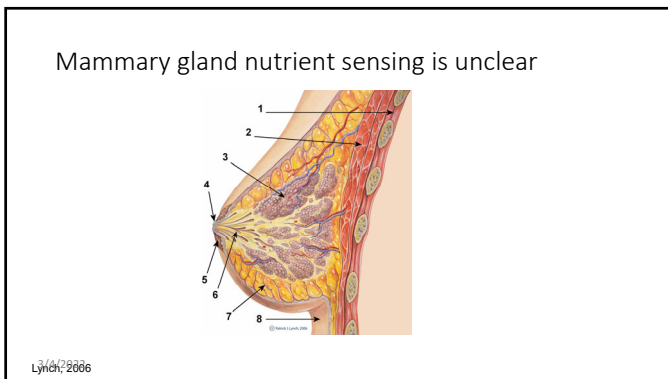
mTORC1 is a nutrient sensor

The mechanistic target of rapamycin 1 (mTORC1) is a nutrient sensor in most cells

Increased mTORC1 activity in visceral fat compartment in obesity

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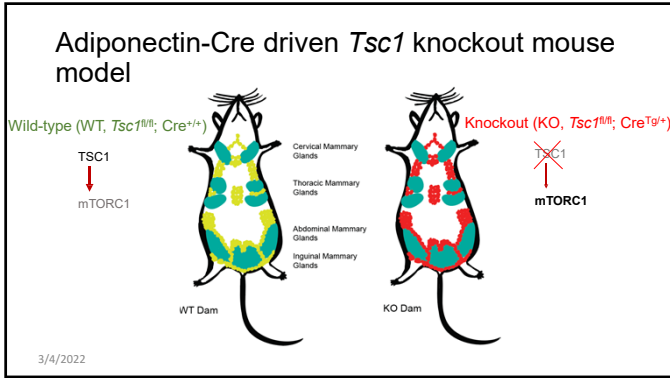
We aimed to understand the role of mammary adipocyte mTORC1 signaling on lactation

Used an Adiponectin-Cre driven *Tsc1* knockout in mice

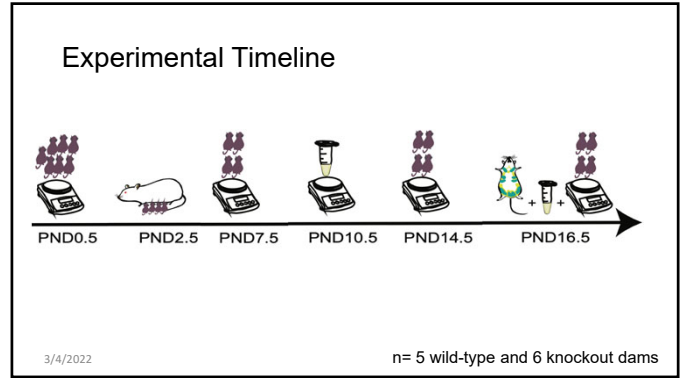
- Mammary gland morphology
- Milk macronutrient composition
- Offspring weight

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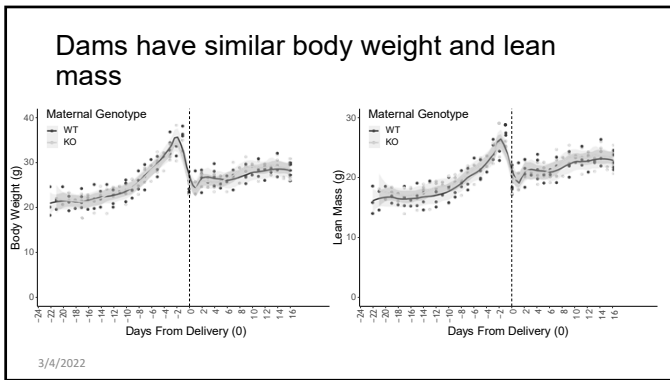
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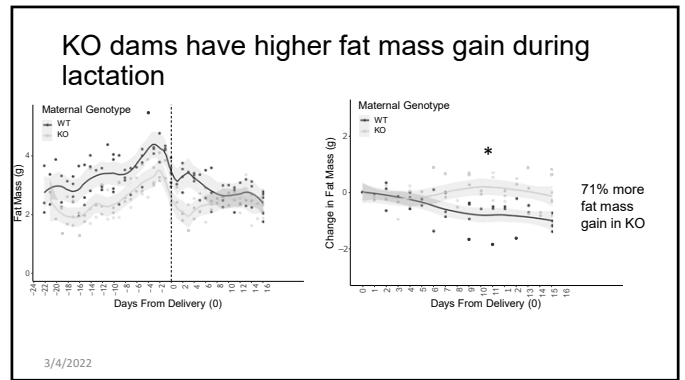
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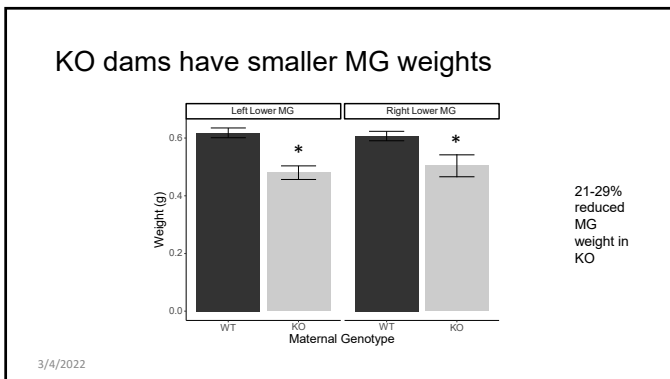
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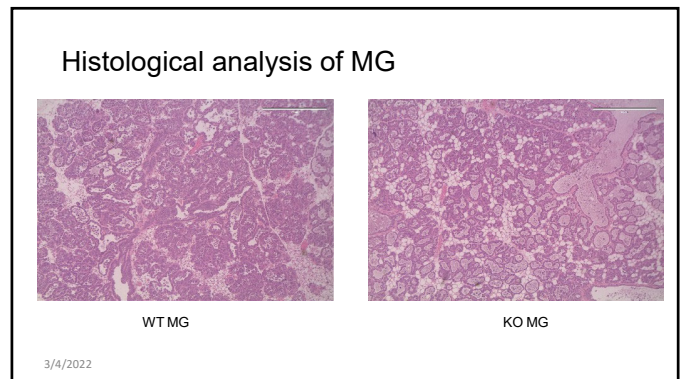
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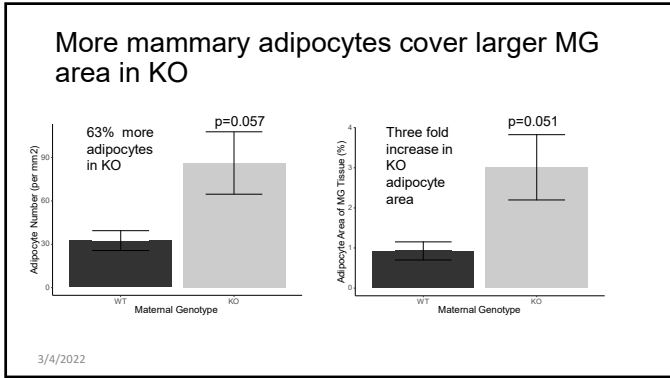
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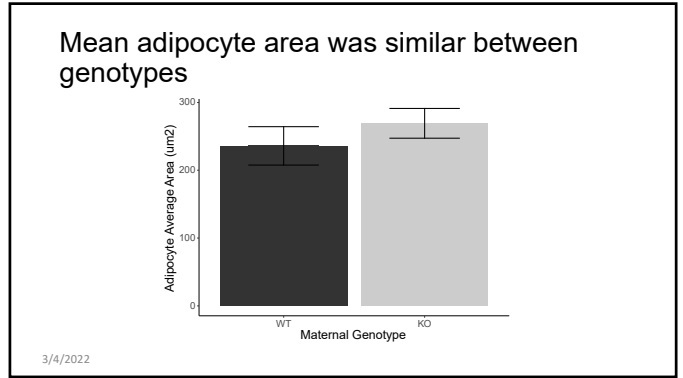
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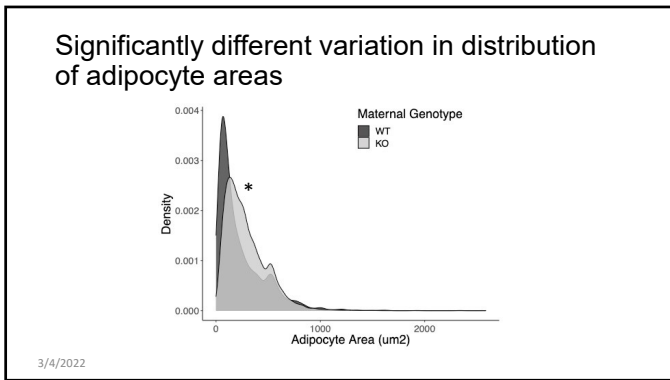
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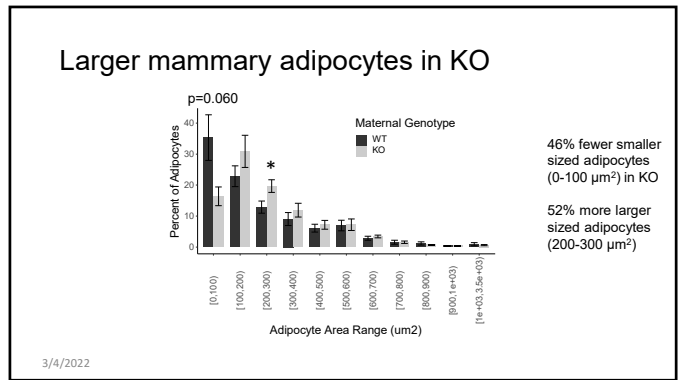
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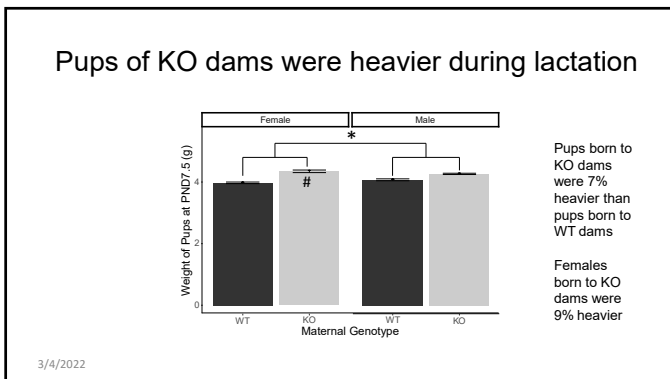
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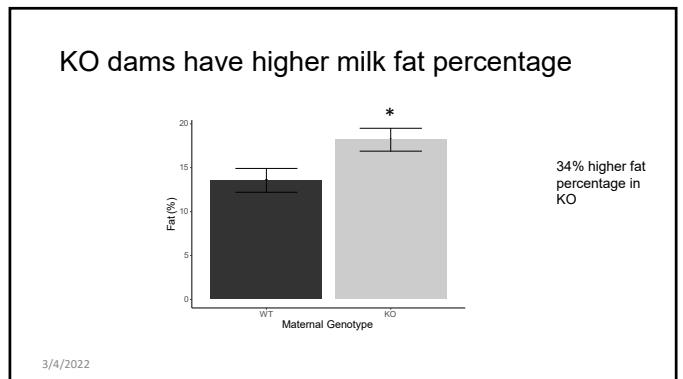
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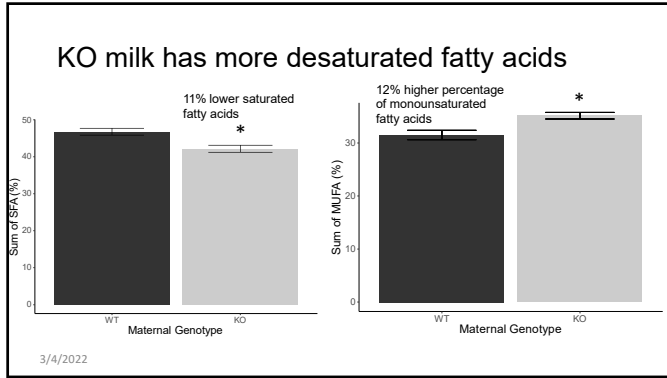
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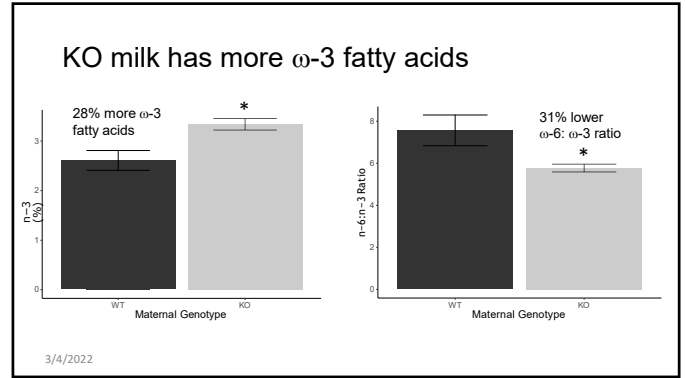
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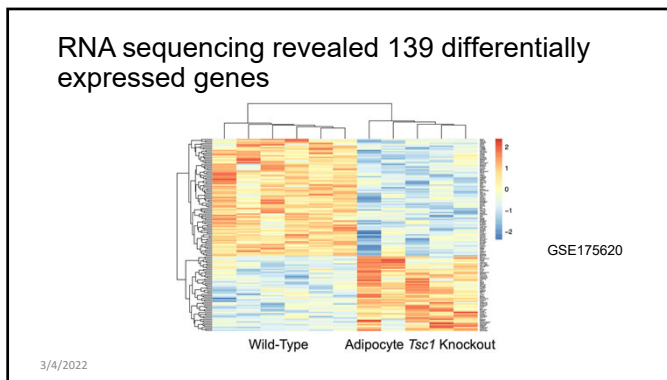
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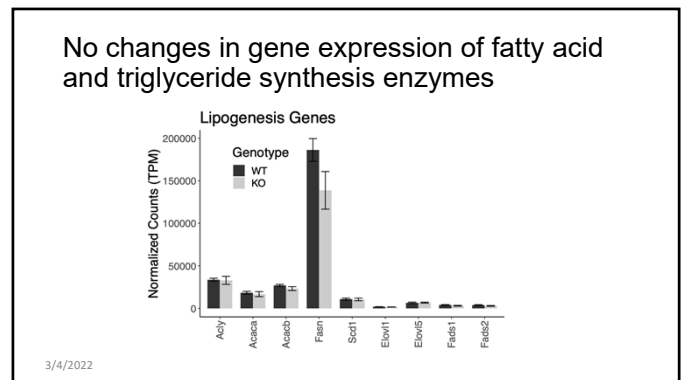
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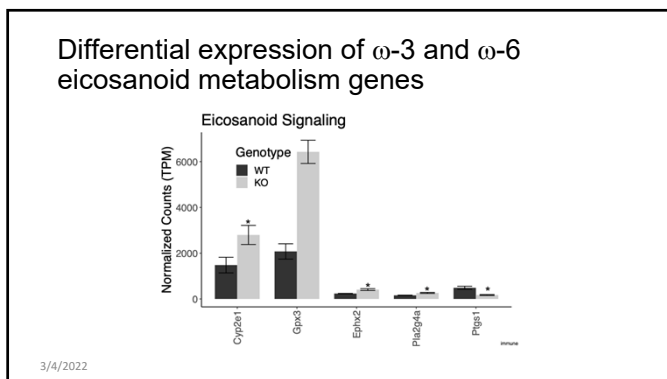
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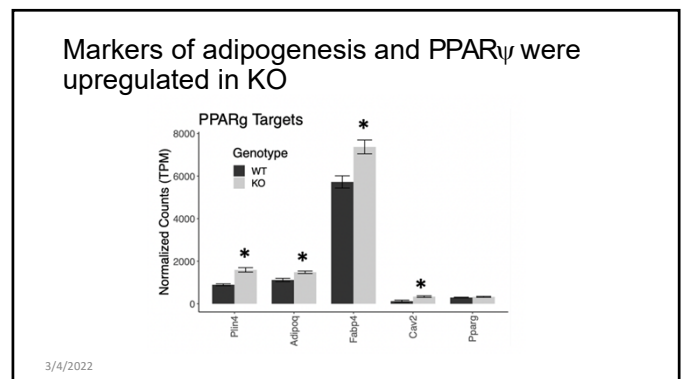
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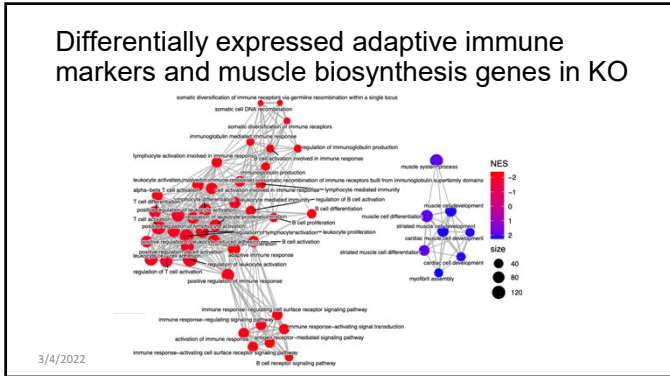
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Summary

- mTORC1 hyperactivation in adipocytes alters MG morphology, milk composition, and whole MG gene expression
- mTORC1 hyperactivation increases milk lipids, fatty acid desaturation and n-3 fatty acid levels, and ultimately, offspring weight
- mTORC1 hyperactivation did not significantly alter expression of lipogenic genes but suppressed expression of adaptive immune markers, and increased expression of muscle biosynthesis genes

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What are some public health implications?

- Breastfeeding remains the golden standard for infant nutrition, but it is important to examine the role of maternal obesity, health, and diet on infant health.
- Around 20% of infants receive infant formula within the first 2 days of life, and 46.9% of infants are exclusively breastfed within the first 3 months of life. It is thus important to incorporate our findings into formula milk engineering to ensure optimal infant growth and availability of essential fatty acids that promote a healthy start of life.

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Exploratory Analysis of the Association Between Breast Milk Lipids and Infant Adiposity

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Breast milk fatty acids impact infant adiposity

- 8% of infants <2YO have high WFL z-scores
- Rapid weight gain during first months of life positively associated with childhood obesity
- Recent evidence suggest that breast milk lipids play a role in infant adipose tissue development
- Conflicting results on the directionality of the association between FAs and adiposity

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We aimed to perform an exploratory analysis to determine associations between breast milk fatty acids and WFL z-scores

- Looking at 2 time points : 2 weeks and 2 months postpartum
- Determining associations with WFL z-scores at 2, 6, 12, and 24 months of age

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Methods

Infant Metabolism And Gestational Endocrinopathies (IMAGE Study)

Mother-infant dyads (n=48-60)

Milk samples were collected at 2 weeks (2w) and 2 months (2m) as a morning collection emptying an entire single breast

Milk analyses: mid-infrared spectroscopy macronutrient analyzer (MIRIS HMA)

Conducted milk lipidomic analyses via gas chromatography to yield fatty acid concentrations, but we present the data here as percentages of long chain fatty acids

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Participant demographics and characteristics

Variable	Participant characteristics with 2 week human milk lipidomic analyses (n=60)	Participant characteristics with 2 month human milk lipidomic analyses (n=48)
Maternal Age (Ethnicity %)	31.22 (0.48)	31.42 (0.53)
Caucasian	41 (68)	33 (69)
African American	3 (5)	4 (8)
Hispanic	6 (10)	4 (8)
Asian	6 (10)	4 (8)
Other/Not Available	4 (7)	3 (6)
Health Condition (%)		
Healthy	32 (53)	22 (46)
Gestational Diabetes Mellitus	7 (12)	8 (17)
Obesity	14 (23)	13 (27)
Polycystic Ovary Syndrome	7 (12)	5 (10)
Parity	1.75 (0.13)	1.78 (0.13)
Maternal BMI	26.53 (0.76)	27.67 (0.86)
Gestational Age	39.73 (0.14)	39.54 (0.16)
Delivery Method (%)		
Vaginal	40 (67)	31 (65)
Cesarean	20 (33)	17 (35)
Infant Sex (%)		
Male	27 (45)	24 (50)
Female	33 (55)	24 (50)

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Milk energy, macronutrients and fatty acid composition

MIRIS Component	2 week values	2 month values
Energy (kcal/100ml)	69.86 (1.34)	68.40 (1.83)
Carbohydrate (g/100ml)	7.00 (0.04)	6.90 (0.10)
True Protein (g/100ml)	1.20 (0.02)	0.92 (0.05)
Fat (g/100ml)	3.81 (0.14)	3.85 (0.20)
Sum Total LCFA (nmol)	1554.24 (61.18)	1522.09 (85.59)
Fatty Acid Categories (nmol)		
Saturated Fatty Acids	541.18 (22.27)	521.65 (32.29)
Monounsaturated Fatty Acids	689.71 (28.66)	659.49 (38.89)
Polyunsaturated Fatty Acids	323.35 (16.22)	340.95 (20.54)
Omega-3 Fatty Acids	23.52 (1.58)	23.65 (1.61)
Omega-6 Fatty Acids	294.24 (14.67)	312.69 (18.99)
Omega6:omega3 Ratio	13.66 (0.57)	14.80 (1.00)

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Levels of seven fatty acids significantly decreased from 2 weeks to 2 months

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Multiple fatty acids were associated with WFLZ

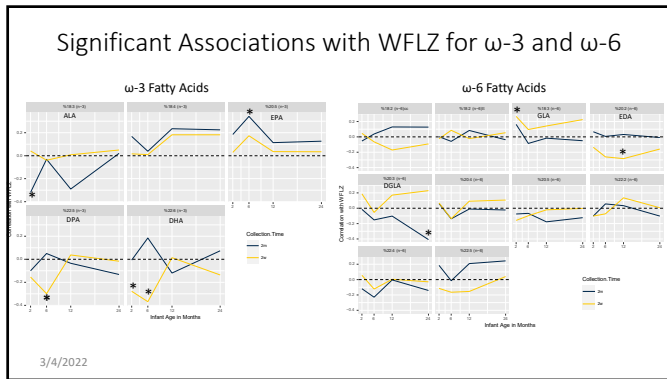
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Significant Associations with WFLZ for SFAs and MUFAs

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Summary

- Levels of seven fatty acids decreased from 2 weeks to 2 months
- There are various significant correlations between milk fatty acid levels at two weeks and two months and WFLZ at 2, 6, 12, and 24 months of age

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What are some public health implications?

- It is crucial to understand the growth trajectories of infants as they can be predictive of adult health (lactational programming).
- These findings provide crucial data to ensure formula milk components are matched with infant needs to ensure optimal and gradual infant growth, as many infants are not breastfed.

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Conclusion

- We show that excess nutrient sensing increases offspring weight and milk fat content
- We show several associations between milk fatty acids and infant adiposity
- Taken together, the data presented clearly demonstrate the important role of early life exposures and nutrition on offspring health

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Future work is needed

- To elucidate mechanisms by which mammary gland nutrient sensing affects the maternal-milk-offspring triad and affects offspring health
- To determine the role of milk fatty acids in infant fat deposition and growth among exclusively breastfed infants and a larger sample size

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Thank you!

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Questions?

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