Lifecourse Epidemiology of Adiposity & Diabetes (LEAD) Center

Summit 2020

October 29th, 10 AM – 12 PM
Objectives

1. Provide history and overview of the LEAD Center
2. Showcase our strengths and accomplishments
3. Generate novel ideas and form new collaborations for the future
Schedule

10 – 10:15 AM        Director’s welcome
10:15 – 10:25 AM     Administrative overview
10:25 – 11:05 AM     Presentation of scientific tracks
11:05 – 11:15 AM     Data core & biorepository
11:15 – 11:45 AM     Breakout session
11:45 AM – 12 PM     Conclusions & adjourn
Director’s welcome

Dana Dabelea, MD PhD
Conrad M. Riley Professor of Epidemiology and Pediatrics
Since the 1960s, obesity has increased steadily, with about 20% of youth aged 6-19 being obese (CDC, National Center for Health Statistics, National Health and Nutrition Examination Survey). Type 2 diabetes has also increased by 30% from 2001 to 2009 in youth across all age, sex, and most race/ethnic groups (Dabelea & Mayer-Davis et al., JAMA 2014). There is growing interest in the developmental origins of health and disease framework and increased focus on the lifecourse approach to chronic disease.

High concentrations of glucose, free fatty acids, and amino acids in maternal plasma result in permanent changes in appetite control, neuroendocrine functioning, or energy metabolism in the developing fetus and thus lead to greater adiposity and risk of future obesity and metabolic disease occurring at increasingly younger ages.

The lifecourse approach

SOURCE: Institute of Medicine and National Research Council: Examining a Developmental Approach to Childhood Obesity: The Fetal and Early Childhood Years—Workshop in Brief; March 2015
• **1997**: Diabetes Prevention Program (DPP; PI: Hamman) /Diabetes Prevention Program Outcome Study (DPPOS; PI: Dabelea)

• **2001**: SEARCH for Diabetes in Youth (PI: Dabelea)

• **2005**: Exploring Perinatal Outcomes among Children (EPOCH, PI: Dabelea)

• **2009**: The Healthy Start Study (PI: Dabelea)

• **2012**: Tribal Turning Point (MPIs: Sauder & Dabelea)

• **2015**: Environmental Influences on Child Health Outcomes (ECHO, PI: Dabelea)

• **2020**: Healthy Start Moms (MPIs: Starling & Dabelea)

• **2020**: DiCAYA (MPIs: Crume & Dabelea)
2015

The LEAD Center was launched!
Vision & Mission

• **Vision**: Children and their families live healthy lives without adiposity, diabetes, and their consequences

• **Mission**: To conduct innovative observational, clinical, behavioral, and basic sciences research on risk factors and consequences of obesity and diabetes from gestation to old age.
Goals for the LEAD Center

- Develop an expanded “Colorado Cohort” to identify subsets of youth at higher and lower levels of risk for future disease
- Expand basic science involvement in human lifecourse studies, including ‘omics’, genetics and epigenetics, microbiome, neurophysiology, pathophysiology, large data integration
- Expand social science involvement in human lifecourse studies to better characterize the social and family influences on development
- Develop and use advanced biostatistical methods for complex lifecourse analyses from subcellular to community levels
- Begin obesity prevention trials during pregnancy and early childhood
- Disseminate findings and implement programs in high risk communities (American Indians, Hispanics, etc.)
How is the LEAD Center achieving our goals?

Training the next generation of researchers

*since 2015: 7 PhD students, 10 postdocs, 12 junior faculty*

- Large Longitudinal cohorts (*Healthy Start, EPOCH*)
- National/International Consortia: ECHO (Environmental Influences on Child Health Outcomes) consortium
- PACE (Pregnancy and Childhood Epigenetics)
- Mechanisms (multi-omics; mesenchymal stem cells)
- Population-based surveillance of pediatric diabetes (*SEARCH*)
- National cohort followed into adulthood
- Clinical trials focusing on obesity/diabetes prevention (*DPP/OS*)
- Translate efficacious clinical trials into effective community prevention (*Tribal Turning Point*)

Welcome  Administration  Scientific tracks  Data core  Breakout Session  Conclusion
How is the LEAD Center achieving our goals?

• 8 active/federally funded research studies that span the lifecourse

• 4 scientific tracks to address important questions:
  – Basic sciences
  – Environmental health
  – ‘Omics
  – Translation

• 2 Support Cores:
  – Data core
  – Administrative core and Pre/Post award management
The lifecourse approach
The Healthy Start Study

EXPOSURES

- & peri-natal
  Maternal behaviors
  Environmental exposures
  Sociodemographic factors

Infancy
- Maternal behaviors
- Environmental exposures
- Sociodemographic factors
- Feeding practices

Childhood
- Behaviors
- Environmental exposures
- Sociodemographic factors
- Family environment
- Sleep habits & function

Adolescent & adulthood
- Behaviors
- Environmental exposures
- Sociodemographic factors
- Family environment
- Sleep habits & function

MECHANISMS

- Maternal metabolic health
- Infant body composition
- Cord blood biomarkers

- Body composition
- Cognition

- Body composition
- Glycemic & metabolic traits
- Cognition

- Adiposity
  Body composition
  Glycemic & metabolic traits
  Hormones
  Cognition

OUTCOMES

Welcome
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The Healthy Start Study

• **Design**: pre-birth cohort of ~1,400 mothers and offspring recruited from University Hospital
  • Participants followed from 1st trimester of pregnancy through delivery and into childhood (currently age 8-10 years)

• **Exposures**: maternal and early life environment (obesity, weight gain, diet, physical activity, smoking (including marijuana), environmental chemicals, depression, stress, social determinants
  • Interest in mechanisms: placental tissue, mesenchymal stem cells, epigenetics, and metabolomics

• **Outcomes**:  
  • Offspring adiposity and cardiometabolic markers  
  • Infant/childhood behaviors: feeding practices, diet, sleeping and physical activity, satiety  
  • Brain development and neuro-cognitive outcome  
  • Respiratory and allergic disease  
  • Food allergies

• Part of NIH-funded ECHO consortium  
• New: Healthy Start moms
Key findings from Healthy Start

• Maternal obesity and gestational weight gain are related to infant adiposity
  • Each 1 kg/m\(^2\) BMI \(\rightarrow\) + 0.12% neonatal fat mass (Starling et al. *AJCN*, 2015)
  • Each 0.1 kg/week of weight gain \(\rightarrow\) + 0.6% neonatal fat mass, independent of pre-pregnancy BMI (Starling et al. *Am J Clin Nutr.*, 2015)
  • *In vitro study*: the relationship between maternal obesity and neonatal adiposity may transpire from greater lipid accumulation, lower fatty acid oxidation, and suppressed AMPK activity (Boyle et al. *Molec Metab* 2016)

• Healthy diet and physical activity are protective
  • Neonates of mothers in the highest compared with the lowest quartile of total energy expenditure during late pregnancy had 41.1 g less fat mass (Harrod et al. *AJOG*, 2014)
  • Neonates of mothers with Healthy Eating Index score >57 vs. <57 had ~ 1% less body fat (Shapiro et al. *IJO* 2016)
Key findings from Healthy Start

• Neonatal adiposity tracks into childhood
  • Each 1 SD increment in neonatal adiposity → 0.12 units higher BMI and ~20% higher prevalence of overweight/obesity between 2 to 6 years of age (Moore et al. Pediatrics 2020)

• The relationship between maternal hyperglycemia and offspring glucose-insulin homeostasis is not completely mediated by child adiposity
  • Children of women in the highest vs. lowest tertile of HbA1c had 0.17 mmol/L higher fasting glucose at age 4-7 years. Adjustment for % fat mass at birth, at 4-7 years, and cumulative fat mass (average) did not change these findings (Francis et al. Diabetologia 2020)
Exploring Perinatal Outcomes among Children (EPOCH)
Exploring Perinatal Outcomes among Children (EPOCH) Study

• **Design**: Historical prospective cohort that recruited youth (N~600) whose mothers were exposed/not-exposed to maternal diabetes in utero

• **Exposure**: Maternal obesity and diabetes/GDM

• **Outcomes**:
  - Offspring adiposity and cardiometabolic biomarkers at 6-14 years and 12-19 years
  - MRI for visceral and subcutaneous fat at 12-19 years
  - Weight and height/length abstracted from medical records starting at birth
  - Interest in mechanisms: genetics, epigenomics, metabolomics, microbiome

• **Future follow up** in young adulthood (submitted grant)
Key findings from EPOCH

• Exposure to GDM influences BMI growth (Crume et al. J Pediatr. 2011)

![BMI Growth Trajectory from Birth through 26 Months](image1)

Effect of Exposure
Average BMI: p=0.53
BMI trajectory: p=0.48

![BMI Growth Trajectory from 27 Months to 13 Years](image2)

Effect of Exposure
Average BMI: p=0.01
BMI trajectory: p=0.008

Diabetes during pregnancy
No diabetes
Key findings from EPOCH

• Maternal GDM is associated with higher adiposity and worse cardiovascular and metabolic profile in offspring
  • 1.28 kg/m² higher BMI, 0.03 units higher waist:height ratio, 4.81 units higher visceral adipose tissue from childhood through adolescence (Hockett et al. Diabetologia 2019)
  • 0.38 mmol/L higher total cholesterol, 0.34 mmol/L LDL in girls; 4.50 mmHg higher SBP in boys from childhood through adolescence (Perng et al. Pediatr Obes 2020)
  • 18% higher HOMA2-IR, 19% lower Matsuda index, and 9% higher HOMA2-β (Sauder et al. Diabet Med. 2017)
  • Potential mechanism: Altered phospholipid metabolism may represent on pathway through which maternal GDM influences offspring adiposity and cardiometabolic health (Perng et al. Diabetologia 2020)

• Maternal obesity is associated with fatty liver in offspring
  • Maternal BMI >30 vs. <25 kg/m² is associated with 1.59% higher hepatic fat fraction (Bellatorre et al. J Pediatr 2018)
SEARCH for Diabetes in Youth

**Exposures**

- **Pre- & peri-natal**
  - Maternal behaviors
  - Environmental exposures
  - Sociodemographic factors

- **Infancy**
  - Maternal behaviors
  - Environmental exposures
  - Sociodemographic factors
  - Feeding practices

- **Childhood**
  - Behaviors
  - Environmental exposures
  - Sociodemographic factors
  - Family environment
  - Sleep habits & function

- **Adolescent & adulthood**
  - Behaviors
  - Environmental exposures
  - Sociodemographic factors
  - Family environment
  - Sleep habits & function

**Mechanisms**

- Maternal metabolic health
- Infant body composition
- Cord blood biomarkers

- Body composition
- Cognition

**Outcomes**

- Body composition
- Glycemic & metabolic traits
- Cognition

- Adiposity
- Body composition
- Glycemic & metabolic traits
- Hormones
- Cognition
SEARCH for Diabetes in Youth

• **Design:**
  • **Registry study** comprising 5 U.S. centers (Colorado including Navajo Nation, Seattle, Cincinnati, Kaiser Southern CA, South Carolina) to identify all youth with diabetes diagnosed 0-19 years of age in a population of ≈5 million, from 2001-2020
  • **Prospective cohort** of ≈3,000 youth with diabetes after onset

• **Goals:**
  • **Registry study:** Define burden of diabetes in youth, and assess time trends by diabetes type
  • **Cohort study:** Identify risk factors, mechanisms, complications, transition to adult care, quality of care, quality of life, mortality

• **Ancillary studies:** SEARCH Case-Control; SEARCH CVD; SEARCH Nutrition; SEARCH Air Pollution; SEARCH Food Insecurity; SEARCH-India

• **DiCAYA**- New surveillance efforts in youth and young adults
SEARCH for Diabetes in Youth

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Key findings from SEARCH

Trends in prevalence of T1D in youth <20 years by sex, age, and race

30.4% relative increase

Source: Dabelea et al., *JAMA*, 2014
Key findings from SEARCH

Trends in prevalence of T1D in youth <20 years by sex, age, and race

35% relative increase

Prevalence per 1,000

Source: et al., JAMA, 2014
Key findings from SEARCH

Trends in incidence of Diabetes in youth <20 years by type and race

Figure 1. Model-Adjusted Incidence Estimates.

Mayer-Davis, et al. NEJM 2017; 376:1419-1429
Key findings from SEARCH

Prevalence of diabetes-related complications and comorbidities in youth with diabetes

<table>
<thead>
<tr>
<th>Complication</th>
<th>Age-Adjusted Prevalence, %</th>
<th>Absolute Difference, % (95% CI)</th>
<th>P Value</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic kidney disease</td>
<td>19.9</td>
<td>5.8</td>
<td>14.0</td>
<td>19.9</td>
<td>.001</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>9.1</td>
<td>5.6</td>
<td>3.5 (0.4 to 7.7)</td>
<td>.02</td>
<td>2.24 (1.11-4.50)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17.7</td>
<td>8.5</td>
<td>9.2 (4.8 to 14.4)</td>
<td>&lt;.001</td>
<td>2.52 (1.43-4.43)</td>
</tr>
<tr>
<td>Cardiovascular autonomic neuropathy</td>
<td>15.7</td>
<td>14.4</td>
<td>1.2 (-3.1 to 6.5)</td>
<td>.62</td>
<td>0.98 (0.57-1.67)</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>47.4</td>
<td>11.6</td>
<td>35.9 (29.0 to 42.9)</td>
<td>&lt;.001</td>
<td>1.07 (0.63-1.84)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.6</td>
<td>10.1</td>
<td>11.5 (6.8 to 16.9)</td>
<td>&lt;.001</td>
<td>0.85 (0.50-1.45)</td>
</tr>
</tbody>
</table>

Dabelea, et al. JAMA 2017; 317(8):825-835
Tribal Turning Point (TTP)

• **Design**: Randomized trial

• **Exposure**: Three-component, culturally-sensitive behavioral intervention among American Indian Youth

• **Outcome**: Obesity and metabolic biomarkers
Diabetes Prevention Program Outcomes Study (DPPOS)
Design: Prospective follow-up of a randomized trial of ~3,100 overweight adults with impaired glucose tolerance

Exposure: Intensive lifestyle intervention or Metformin (vs. placebo group)

Outcomes: Diabetes and diabetes complications, cardiovascular disease, cancer, mortality, multimorbidity, quality of life
  • Followed for 3 years in active trial
  • Followed for up to 18 years in DPPOS
Key findings from DPPOS

• Prevention or delay of T2D with lifestyle intervention or metformin in a high-risk population can persist for over 18 years
  • Intensive lifestyle changes aimed at modest weight loss reduced rate of developing T2D by 34%, and delayed onset by 4 years
  • The lifestyle changes also reduced CVD risk factors, HbA1C, and fasting glucose in comparison to placebo
  • Treatment with metformin reduced rate of developing diabetes by 18%, delayed diabetes by 2 years, and reduced HbA1c and fasting glucose.
LEAD research in the spectrum of translation

Clinical Translational Research Spectrum

Scientific discovery  Pre-clinical insights  Clinical insights  Implications for practice  Population health  Global health

Translation to animal models  Translation to humans  Translation to patients  Translation to practice  Translation to population

Adapted from the Center for Clinical and Translational Science Institute
What we have done and where to go next?

- Expand basic science involvement in human lifecourse studies, including ‘omics’, genetics and epigenetics, microbiome, neurophysiology, pathophysiology, large data integration

- Expand social science involvement in human lifecourse studies to better characterize the social and family influences on development

- Develop and use advanced biostatistical methods for complex lifecourse analyses from subcellular to community levels

- Begin obesity prevention trials during pregnancy and early childhood

- Disseminate findings and implement programs in high risk communities (American Indians, Hispanics, etc.)

- Develop an expanded “Colorado Cohort” to identify subsets of youth at higher and lower levels of risk for future disease

4 scientific tracks

Recruitment of trainees, collaborations in SEARCH and ECHO

Collaborations with biostatisticians and basic sciences colleagues

TTP, SEARCH

Healthy Start
Schedule

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Administrative overview

Lisa Testaverde, MS
Assistant Director, Research Administration
Administrative overview

Personnel

• **Grants Administration**: Lisa Testaverde and Allison McCawley

• **Project Management**: Anna Bellatorre, Brandy Ringham, Mercedes Martinez, Jennifer Truong, Rachel Steinberg
Administrative overview

Grants Administration

• **Pre-award** (grant and subcontract applications, budget, budget justification, routing, submission)

• **Post-award** (account set up, expenditure tracking, financial reporting, subcontract agreements and monitoring, invoicing and payments, journal entries, progress reports)

• **Payroll and Human Resources** (job postings and on-boarding, funding distribution, PETs)
Administrative overview

Project Management

• PhD and Master’s level project managers

• IRB submissions, DUAs, staff training and management, oversight of daily operations, protocol compliance, SAE tracking, expenditure tracking, supply purchasing
Administrative overview

Grant Funding

LEAD Proposals since 2015

- 80 funding proposals submitted
- 91% to Federal sponsors
- # proposals submitted through CSPH = 53 and through PEDS = 27
- Funding rate = 30.0%
Administrative overview

Currently active projects

24 awards totaling $5.5M in direct costs

• 6 U grants
• 6 R01 grants
• 1 K99/R00 grant
• 1 KL2 career development award through CCTSI
• 2 post-doctoral fellowship awards through Pediatrics T32
• 6 subcontracts
• 2 foundation awards
Administrative overview

THE FUTURE

• Anschutz Health Sciences Building

• LEAD Center occupies 10,000+ sq ft on 1st floor

• Move-in projected Fall 2021!
# Schedule

<table>
<thead>
<tr>
<th>Time</th>
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</tbody>
</table>
Scientific Track 1 | Basic sciences

Director: Kartik Shankar PhD, Professor of Pediatrics
Scientific Track 1 | Basic sciences

- Cohorts
- Tissues, Cells & Biospecimens
- Experimental Models
- Multi-omics
  - Lipids
  - Metabolites
  - Transcriptome
  - Epigenome
  - Maternal info
  - Lipidomics
  - Metabolomics
  - RNA-seq
  - EPIC
Scientific Track 1 | Basic sciences

- Healthy Start

- ECHO – Aim 2
- Boyle Lab – Mesenchymal Stem Cell Projects
**Scientific Track 1 | Basic sciences**

**ECHO Aim 2**

- Myself, Ivana Yang, Katerina Kechris, Thomas Jansson, Jed Friedman
  - Madeline Keleher (postdoc), Cheyret Wood (Research Instructor), Sierra Niemiec (PRA)

- **Goal:** To measure molecular signatures associated with prenatal environmental exposures to determine biological pathways linking these exposures with child outcomes

- **Biological Samples**
  - Placenta
  - Umbilical cord blood
  - Infant mesenchymal stem cells
## Scientific Track 1 | Basic sciences

### ECHO Aim 2 – samples & data

<table>
<thead>
<tr>
<th></th>
<th>Cord Blood</th>
<th>Placenta</th>
<th>MSC</th>
<th>Sample Overlap</th>
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</thead>
<tbody>
<tr>
<td>DNA Methylation</td>
<td>450K</td>
<td>EPIC Array</td>
<td>EPIC Array</td>
<td>CB + plac. n=65, CB + MSC n=41</td>
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<tr>
<td></td>
<td>Samples = 600</td>
<td>Samples = 97</td>
<td>Samples = 62</td>
<td></td>
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<tr>
<td>Metabolomics</td>
<td>Samples = 49</td>
<td>Samples = 38</td>
<td>Samples = 54</td>
<td>CB + plac. n=29, CB + MSC n=42</td>
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<tr>
<td></td>
<td>Metabolites = 652</td>
<td>Metabolites = 630</td>
<td>Metabolites = 1,053</td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
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<td>Samples = 109</td>
<td>Samples = 131</td>
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<td>Proteins = 20</td>
<td>Proteins = 3</td>
<td>Proteins = 2</td>
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<tr>
<td>RNAseq</td>
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<td>none</td>
<td>Samples = 142</td>
<td>n/a</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Genes = 15,970</td>
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</table>
Scientific Track 1 | Basic sciences

ECHO Aim 2 – Current Projects

• Association of placental protein content with maternal metabolic markers and offspring body composition published, under review

• Multi-omic/multi-tissue analysis of association with maternal metabolic markers and offspring body composition analysis

• Secondary analyses
  • Nicholas Broskey, PhD Assistant Professor, East Carolina University
    • Maternal physical activity and infant MSC outcomes
  • Ellen Francis, PhD and Wei Perng, PhD LEAD Center
    • Gestational diet quality and sexually dimorphic effects on metabolic pathways in placenta and infant MSCs
Scientific Track 1 | Basic sciences
Boyle Lab – Mesenchymal Stem Cell Studies

MSCs

- Adipocytes
- Osteocytes
- Myocytes
- Chondrocytes

Adipose
Bone
Muscle
Cartilage
**MSC Studies: Maternal Obesity**

- **Maternal obesity alters fatty acid oxidation, AMPK activity, and associated DNA methylation in mesenchymal stem cells from human infants**

**Mesenchymal Stem Cells From Infants Born to Obese Mothers Exhibit Greater Potential for Adipogenesis: The Healthy Start BabyBUMP Project**

- **GSK-3β/β-catenin**

- **Lipid Content**
- **Lipid Oxidation**

- **Metabolically Healthy**
- **Metabolically Unhealthy**

**Maternal obesity and increased neonatal adiposity correspond with altered infant mesenchymal stem cell metabolism**

**Scientific Track 1 | Basic sciences**

**Diabetes** Volume 65, March 2016

Kristen E. Boyle, Zachary W. Patinkin, Allison L.B. Shapiro, Peter R. Baker II, Dana Dabelea, and Jacob E. Friedman

**Diabetes** 2016;65:473-483. DOI: 10.2337/db15-0849

**Original Article**

**PLOS ONE**

Rebecca J. Ford, Benjamin M. Wright, Deborah H. Osicka, Linda A. Bardos, Jill M. Necas, and Jacob E. Friedman

**RESEARCH ARTICLE**

Nicotinamide Promotes Adipogenesis in Umbilical Cord-Derived Mesenchymal Stem Cells and Is Associated with Neonatal Adiposity: The Healthy Start BabyBUMP Project

**RESEARCH ARTICLE**

Maternal obesity and increased neonatal adiposity correspond with altered infant mesenchymal stem cell metabolism

**Welcome**

**Administration**

**Scientific tracks**

**Data core**

**Breakout Session**

**Conclusion**

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MSC Studies: Adipocyte hypertrophy

Hyperplasia or Hypertrophy

Healthy AT expansion

Macrophage infiltration
Oxidative stress
Systemic glucose intolerance

2-dimensional

3-dimensional

Kristen Boyle, PhD | Associate Professor of Pediatrics, Section of Nutrition

Welcome | Administration | Scientific tracks | Data core | Breakout Session | Conclusion

Keleher et al., In Preparation, 2020.
Scientific Track 1 | Basic sciences

MSC Studies: Current Data Collection

• MSC metabolism and response to metabolic stress during myogenesis in vitro American Diabetes Association CORE Award
  • In depth metabolic phenotyping in the context of maternal obesity
  • Characterization of metabolism across all MSC samples for association studies

• Epigenetic regulation of metabolism in MSCs undergoing myogenesis in vitro NIDDK R01
  • Role of DNA methylation in regulating metabolic phenotype in MSCs
    • Differential methylation of 2 specific genes previously identified.
Scientific Track 2 | Environmental health

Director: Anne Starling PhD, Assistant Professor of Epidemiology
Scientific Track 2 | Environmental health

What do we do?

While LEAD considers the totality of the “environment” of development, our group has a specialized focus on how exposures in the chemical and physical environment may influence the development of adiposity and metabolic disease throughout the lifecourse.
Scientific Track 2 | Environmental health

What do we do?

Ancillary studies to LEAD cohorts have enabled collection of extensive environmental exposure data:

- **Air pollution**
  - Traffic related air pollution using GIS data and regulatory monitors
  - Black carbon spatiotemporal model, including new monitoring at residences supported by NIH ECHO (Subcontract PI: Magzamen)

- **Tobacco smoke exposure**
  - Cotinine in maternal urine during pregnancy
  - Biomarkers of childhood secondhand smoke exposure in urine

- **Chemical exposures with widespread exposure in the general population via drinking water and consumer products:**
  - Maternal serum perfluoroalkyl substances (PFAS) and urinary phthalates and phenols, organophosphate flame retardants, metals
Combined environmental and social exposures during pregnancy and associations with neonatal size and body composition

The Healthy Start study

Sheena E. Martenies, William B. Allshouse, Anne P. Starling, Brandy M. Ringham, Deborah H. Glueck, John L. Adgate, Dana Dabelea, Sheryl Magzamen.
What will we do next?

• Newly funded R01 from the National Institute of Environmental Health Sciences (NIEHS) and the Office of Research on Women’s Health (ORWH) to examine the effects of environmental chemical exposures during pregnancy on short-term and long-term cardio-metabolic health in mothers previously enrolled in the Healthy Start study.

• Other grants submitted/in development continue to investigate pathways/mechanisms by which environmental exposures in utero and in early childhood lead to later life health outcomes, including:
  • epigenetic changes
  • metabolomic profiles
  • behavioral/neurocognitive changes
Scientific Track 2 | Environmental health
Chloe Friedman, MPH | Mentor: Anne Starling, PhD

Project 1
In utero exposure to air pollution (PM$_{2.5}$ and O$_3$) → Confounders → Inflammatory biomarkers in maternal and cord blood

Project 2
In utero exposure to air pollution (PM$_{2.5}$ and O$_3$) → Confounders → Cardio-metabolic markers in cord blood
Scientific Track 2 | Environmental health
Lizan Bloemsma, PhD | Mentor: Anne Starling, PhD

Project 1: Prenatal exposure to ambient air pollution and traffic and indicators of adiposity in early childhood: The Healthy Start study

Outcomes:
Overweight, waist circumference, percent fat mass and fat mass index at age 4-6 years

Conclusions:
• Limited evidence of associations of prenatal exposure to ambient PM$_{2.5}$ and O$_3$ with indicators of adiposity in early childhood among mother-child pairs in a low exposure setting
• Suggestive associations of residential proximity to a highway during pregnancy with greater adiposity merit further investigation
Exposure assessment in the Healthy Start study:
- Neighborhood walkability
- Ambient air pollution - CACES LUR models
- Green space
Scientific Track 2 | Environmental health

Lizan Bloemsma, PhD | Mentor: Anne Starling, PhD

Current and future projects:
In daily life, people are simultaneously exposed to a wide range of environmental factors that could affect health

→ Examining the health effects of multiple, spatially correlated environmental exposures in one study

• Green space, air pollution, neighborhood walkability and cardiometabolic health during pregnancy

• Other health outcomes: cardiometabolic health in early childhood, growth trajectories
Scientific Track 3 | The ‘omics cascade

Genomics

Epigenomics

Transcriptomics

Proteomics

Metabolomics

Microbiome

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Scientific Track 3 | Metabolomics

- Diet
- Physical activity
- Environmental toxicants
- Pharmaceutical & drug use
- Smoking
- Internal processes
  - Genome
  - Metabolome
  - Epigenome
  - Transcriptome
  - Proteome
  - Metabolite

Breakout Session

Welcome | Administration | Scientific tracks | Data core | Breakout Session | Conclusion
In utero exposures
- Maternal behaviors
- Environmental exposures
- Intrauterine environment

Biosamples in mother:
- Maternal plasma/serum
- Urine
- Placenta tissue
- Amniotic fluid
- Cord blood
- Breastmilk
- Solid tissues (hair, nails, adipose)

Birth outcomes
- Fetal growth
- Body composition

Infancy exposures
- Feeding practices
- Environmental exposures

Biosamples in infant:
- Plasma/serum
- Urine
- Solid tissues (hair, nails, adipose)

Infancy outcomes
- Body composition
- Growth trajectory

Childhood exposures
- Child behaviors
- Environmental exposures

Biosamples in child:
- Plasma/serum
- Urine
- Solid tissues (hair, nails, adipose)

Childhood outcomes
- Body composition
- Growth trajectory
- Cardiometabolic risk biomarkers

Adult outcomes
- MHO vs. MUO
- Body composition
- Cardiometabolic disease biomarkers

Key
1. Capturing exposures
2. Refining outcomes
3. Understanding pathways

Scientific Track 3 | ‘Omics science

- Conceptual framework for dissertation research @ Emory:

Diet Quality

↑ Added sugar

Central Fat Deposition

Visceral fat
Abdominal Subcutaneous Fat
Hepatic fat

Metabolic Dysfunction

Clinical Risk Factors
Metabolomic Pathway Disturbances
Metabolomics profiles across adolescence shed light on unique and shared metabolic perturbations underlying in utero exposure to maternal obesity and gestational diabetes

Objective: leverage untargeted metabolomics data from fasting plasma samples collected at two timepoints (childhood and adolescence) to investigate whether the metabolome of offspring differ by two maternal metabolic phenotypes: GDM without obesity, and obesity without GDM (Francis et al. on going analysis 2020)
Scientific Track 3 | ‘Omics science

- Conceptual framework for dissertation research @ Emory:

**Diet Quality**
- ↑ Added sugar

**Central Fat Deposition**
- Visceral fat
- Abdominal Subcutaneous Fat
- Hepatic fat

**Metabolic Dysfunction**
- Clinical Risk Factors
- Metabolomic Pathway Disturbances
Scientific Track 3 | ‘Omics science

• A) Integrative network analysis of metabolomics x clinical biomarkers x central/ectopic body fat deposition.

• Main findings:
  • Distinct network of clinical and molecular biomarkers clustered more strongly with hepatic fat (vs. VAT and SAT).
  • Included 8 clinical biomarkers and 800+ metabolite features

Cioffi et al., BMJ Open Diabetes Res Care, 2020
Scientific Track 3 | ‘Omics science

• B) Systems biology analysis of “omics” changes (metabolome, microbiome) associated with dietary free sugar restriction in boys with NAFLD.

• Main findings:
  • Differential expression of metabolites enriched in amino acid and lipid metabolism.
  • Microbiome changes related to increased richness and microbial composition.

Cioffi et al., unpublished (manuscript in preparation), 2020
Scientific Track 3 | ‘Omics science

• B) Systems biology analysis of “omics” changes (metabolome, microbiome) associated with dietary free sugar restriction in boys with NAFLD.

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  • Differential expression of metabolites enriched in amino acid and lipid metabolism.
  • Microbiome changes related to increased richness and microbial composition

Cioffi et al., unpublished (manuscript in preparation), 2020
Projects in the LEAD center will focus on determinants and consequences of pediatric NAFLD, and (eventually) interventions for prevention/treatment.

- **EPOCH**: Diet quality in childhood and hepatic fat accumulation in adolescence (12-19 yrs)
- **Healthy Start**: Exposures *in utero* and offspring hepatic fat in childhood (4-7 yrs)
Scientific Track 4 | Translation

Director: Kate Sauder PhD, Assistant Professor of Pediatrics
Scientific Track 4 | Translation

Epidemiology

Observational studies

EPOCH
Healthy Start
SEARCH
DPPOS
Scientific Track 4 | Translation

Epidemiology

Observational studies
- EPOCH
- Healthy Start

Experimental studies
- SEARCH
- DPPOS
Scientific Track 4 | Translation

Translation track
Translate observational findings into prevention strategies with high potential for widespread dissemination and implementation

Epidemiology

Observational studies
- EPOCH
- Healthy Start
- SEARCH
- DPPOS

Experimental studies
- Tribal Turning Point
- NDPP-NextGen

Welcome  Administration  Scientific tracks  Data core  Breakout Session  Conclusion
Scientific Track 4 | Translation

Tribal Turning Point
Reducing diabetes risks in American Indian children

NDPP-NextGen
Reducing weight and diabetes risks before pregnancy
Scientific Track 4 | Translation

Tribal Turning Point
Reducing diabetes risks in American Indian children
American Indian youth disproportionately affected by rising incidence in youth-onset type 2 diabetes

Mayer-Davis et al, New Eng J Med 2017
Tribal Turning Point | Development

Welcome | Administration | Scientific tracks | Data core | Breakout Session | Conclusion
Tribal Turning Point | Program

Welcome
Administration
Scientific tracks
Data core
Breakout Session
Conclusion

Local staff

RED = lichii
Whole foods - high in fat and calories. Eat rarely. STOP and THINK before we eat these foods.

YELLOW = litso
Slow foods - have nutrients but have a little more fat and calories than go foods. Eat sometimes and/or in a smaller amount.

GREEN = dootl'izh
Go foods - low in fat and calories and packed full of vitamins, minerals & fiber. Eat every day.

R34DK096403 (Mayer-Davis, Dabelea)
BMI, BMI z-score, waist circumference improved by TTP intervention compared to control group.
3-site clinical trial
175 enrolled pre-COVID

Rapid transition
remote delivery
no-contact data collection
remote recruitment

R01DK115434 (Dabelea, Sauder)
Tribal Turning Point | Highlights

SUCCESSES

CHALLENGES

Welcome  Administration  Scientific tracks  Data core  Breakout Session  Conclusion
Tribal Turning Point | Highlights

**SUCCESSES**

✓ Secured 10 years of funding
  - NIDDK – R34DK096403 (2013-2016)
  - NIDDK – R01DK115434 (2017-2022)

**CHALLENGES**

- Welcome
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Tribal Turning Point | Highlights

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CHALLENGES
Tribal Turning Point | Highlights

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Tribal Turning Point | Highlights

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**CHALLENGES**

- Recruiting into *randomized* study
  - How to present & facilitate retention in *both* arms

- Program attendance
  - Up to 20 sessions over 12 months
  - Many life changes in this period
  - Low resource community often needs assistance

- COVID
  - In-person activities restricted
  - Family routines disrupted
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Tribal Turning Point | Future

Complete clinical trial in 3 years
• If successful, disseminate program and support local implementation
• If not, consider further refining program/implementation
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Applicability to non-Native rural communities
• Need to reflect on current challenges, address up-front with communities
Tribal Turning Point | Future

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- If successful, disseminate program and support local implementation
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Applicability to non-Native rural communities
- Need to reflect on current challenges, address up-front with communities

Consider sustainability strategies
Scientific Track 4 | Translation

NDPP-NextGen
Reducing weight and diabetes risks before pregnancy
Pre-conception health | Rationale

Exploring Perinatal Outcomes among Children
Pre-conception health | Rationale

Explores Perinatal Outcomes among Children

Pre-birth exposures influence obesity and diabetes risks across the lifecourse
Exploring Perinatal Outcomes among Children

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Prenatal interventions have little effect on gestational weight gain, diabetes
Pre-conception health| Rationale

Exploring Perinatal Outcomes among Children

Pre-birth exposures influence obesity and diabetes risks across the lifecourse

Earlier intervention is needed

Prenatal interventions have little effect on gestational weight gain, diabetes
Pre-conception health | Approach
Pre-conception health | Approach

Diverse women of peak child-bearing:

- Can lose weight (4% at 3mo and 7% at 9mo)
- Can keep weight off until conception (-1.1 kg/m^2)
- Have optimal early pregnancy HbA1c (<5.9%)
Pre-conception health | Approach

Diverse women of peak child-bearing:
- Can lose weight (4% at 3mo and 7% at 9mo)
- Can keep weight off until conception (-1.1 kg/m²)
- Have optimal early pregnancy HbA1c (<5.9%)

Not often referred (~7%)
- Less likely to sign up
- Less likely to show up
- Less likely to come back

Ritchie & Sauder, Am J Prev Med 2017
Scientific Track 4 | Challenges

**Barriers**
- Childcare
- Coach load
- Cultural competence
- In-person class
- Transport
- Day/time options

**Facilitators**
- What to expect
- Coach support
- Group support
- Follow-up
- Referrals
- Personal goals
- Coach support

Harrison et al, Diabetes Educator 2020
Scientific Track 4 | Challenges

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*Harrison et al, Diabetes Educator 2020*
Scientific Track 4 | Challenges

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Harrison et al, Diabetes Educator 2020
Scientific Track 4 | Challenges

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- Follow-up
- Referrals
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- Coach support

*Harrison et al, Diabetes Educator 2020*
Scientific Track 4 | Future

• NDPP-NextGen
  • Enhanced implementation strategy to better serve diverse, under-resourced women
  • Leverages nationally-disseminated, evidence-based program
  • Aims to reduce maternal weight and diabetes risks before pregnancy and, in turn, benefit offspring
**Scientific Track 4**

<table>
<thead>
<tr>
<th>Tribal Turning Point</th>
<th>NDPP-NextGen</th>
</tr>
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<tbody>
<tr>
<td><strong>U of Colorado</strong></td>
<td><strong>U of Colorado</strong></td>
</tr>
<tr>
<td>Dana Dabelea</td>
<td>Caroline Harrison</td>
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<tr>
<td>Richard Hamman</td>
<td>Noy Phimphasone-Brady</td>
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<tr>
<td>Christy Hockett</td>
<td>Denver Health</td>
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<td>John Kittelson</td>
<td>Natalie Ritchie</td>
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<td>Spero Manson</td>
<td>Stefka Fabbri</td>
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<td>Noy Phimphasone-Brady</td>
<td>Silvia Raghuanath</td>
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<td>Danielle Ostendorf</td>
<td>Riley Bright</td>
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<td>Lisa Testaverde</td>
<td>CDPHE</td>
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<td>Rachel Steinberg</td>
<td>Becky DiOrio</td>
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<td>Debra Yazzie</td>
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<td>Kendralyn Begay</td>
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<td>Paula Begay</td>
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<td>Shawna Nelson</td>
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<td>Deidra Goldtooth</td>
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<td>Melanie Aspaas</td>
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<td>Eugena Armijillio</td>
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<td><strong>Navajo</strong></td>
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<td>Jeff Powell</td>
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<td>Roz Barber</td>
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<td>Maria Cassidy-Begay</td>
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<td>Carol Percy</td>
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<td>Janelia Smiley</td>
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<td><strong>NIDDK Phoenix</strong></td>
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<td>Madhumita Sinha</td>
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<td>William Knowler</td>
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<td>Mary Hoskin</td>
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<td><strong>Cherokee</strong></td>
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<td>Robin Bailey Callahan</td>
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<td>Sheena Kanott Lambert</td>
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<td>Rose James</td>
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<td>Cherokee IRB</td>
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<td><strong>U of North Carolina</strong></td>
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<tr>
<td>Elizabeth Mayer-Davis</td>
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<td>Beth Jenks</td>
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<td>Lisa Leteraneau</td>
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<td>Joan Thomas</td>
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<td>Victor Zhong</td>
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<td><strong>University of Miami</strong></td>
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<tr>
<td>Alan Delamater</td>
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</table>
Scientific Track 4 | Translation Impact

LEAD Vision
Families living healthy lives without adiposity, diabetes, or their sequelae
Scientific Track 4 | Translation Impact

LEAD Vision
Families living healthy lives without adiposity, diabetes, or their sequelae

Translate findings into true impact on clinical practice, public health programs
Scientific Track 4 | **Translation Impact**

**LEAD Vision**
Families living healthy lives without adiposity, diabetes, or their sequelae

*NEW* quarterly series:
LEAD Scientific Advisory Forum
Hear directly from potential end-user stakeholders the challenges facing their target populations
Explore together how to leverage LEAD research to improve health

November 17 @ 11 am
Schedule

10 – 10:15 AM  Director’s welcome
10:15 – 10:25 AM  Administrative overview
10:25 – 11:05 AM  Presentation of scientific tracks
11:05 – 11:15 AM  Data core & biorepository
11:15 – 11:45 AM  Breakout session
11:45 AM – 12 PM  Conclusions & adjourn
Data Core and Biorepository

Directors: Deborah Glueck PhD, Professor of Pediatrics
Brandy Ringham PhD, Research Associate & Senior Data Manager
EPOCH: Methodology for defining a new hallmark of skeletal growth

Kylie K. Harrall, Joseph D. Hoffman, Christine W. Hockett, Dana Dabelea, Keith E. Muller, and Deborah H. Glueck

R01GM121081
Known skeletal hallmark: peak height velocity

Important epidemiological associations have been identified using peak height velocity:


Is there another skeletal hallmark between ages 4-6?

Skeletal height velocity slows in early childhood

How can we quantify this slowing in height velocity?

\[ \kappa = \frac{|f''(x)|}{\left(1 + [f'(x)]^2\right)^{3/2}} \]

- Curvature is inversely proportional to the radius of the osculating circle.
- Zero curvature values correspond to straight lines.
- Higher values of curvature correspond to smaller osculating circles with faster changes in the curve.
We defined the hallmark to be the point at which curvature equals 1.
With this definition, the average age at slowed skeletal velocity occurs between ages 4-6.
The new skeletal hallmark helped explain the association between gestational diabetes and BMI.

The effects of exposure to maternal gestational diabetes on offspring BMI and growth trajectories throughout childhood and adolescents: The Exploring Perinatal Outcomes among Children (EPOCH) study
Christine W Hockett PhD, Kylie K Harrall, Deborah H Glueck PhD, Dana Dabelea MD PhD
Manuscript in progress.
Biorepository Inventory

Total Number of Samples
244,881

<table>
<thead>
<tr>
<th>Number of Samples by Study</th>
<th>Number of Samples by Sample Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPOCH</td>
<td>Plasma/Serum</td>
</tr>
<tr>
<td>Healthy Start</td>
<td>DNA/RNA</td>
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<tr>
<td>ECHO</td>
<td>Urine</td>
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<tr>
<td>SEARCH</td>
<td>Placenta/Cord Tissue</td>
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<tr>
<td>Tribal Turning Point</td>
<td>Feces</td>
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<tr>
<td>TODAY</td>
<td>Other</td>
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<td>161,599</td>
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<td>22,853</td>
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Biorepository Projects

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<tr>
<th>Internal</th>
<th>External</th>
<th>ECHO</th>
<th>Total</th>
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<tbody>
<tr>
<td>8</td>
<td>7</td>
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<td>22</td>
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</table>

Biomarkers and mechanisms of NAFLD and T2D pathogenesis in two adolescent cohorts (Wei Perng, University of Colorado Denver)

Mitochondrial DNA and metabolism (Victor Zhong, Cornell University)

Exposures to environmental phenols and asthma risk (Rachel Miller, ECHO)
Project Proposal Guidelines

https://coloradosph.cuanschutz.edu/research-and-practice CENTERS-PROGRAMS/LEAD/RESEARCH/PROJECT-PROPOSAL-GUIDELINES
## Schedule

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<td>Conclusions &amp; adjourn</td>
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Breakout Session
Breakout session

• Smaller groups to ask follow-up questions, explore new ideas
  • “Where are we going next? How do we get there?”
  • After 30 minutes, breakouts will close - back together to share highlights

• Choose the session you want to join
  • Click the “break-out” room function on your screen to move yourself
  • “Chat” your preference to be moved by the host