WE ALL WORK TOGETHER

Patient and clinician contributors!

• PEDSNet Data Sites
  • CHOP (Forrest)
  • CH Colorado (Kahn)
  • Nationwide (Kelleher)
  • Nemours (Milov)
  • Seattle (DelBeccaro)
  • St. Louis (Yu)

• PEDSNet Analytics (CHOP)
  • Tom Richards
  • Chris Forrest
  • Elizabeth Hines

• Obesity and Antibiotics
  • Peixin Zhang
  • Alice Livshits

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DISCLOSURES

• No financial conflicts of interest

• The Healthy Weight program at CHOP has received grant funding from the American Beverage Association. The ABA had no role in any of the work presented here.

• I may mention in passing some pediatric uses of medications that are off-label.
One potential use of learning health systems is that the process of caring for patients generates a lot of data.

Electronic health records make a subset of these data more readily available for learning

- Scale
- Format
- Connections

“Secondary Use”
PEDSnet Obesity Pilot

- PEDSnet is a collaboration of (now) 8 large children’s hospitals to support developing a learning health system for children.
- In 2010, six hospitals decided to look at whether we could learn about childhood obesity using EHR data
  - Technical and scientific test
  - Looked at 2008-2009 outpatient data
  - Goals were to compare to NHANES, and see what clinical information was added
- Ca. 500,000 children, 1.4 million visits
EXTENSIVE DATA ON BMI
Agrees Well with NHANES
### Similar Prevalence of Obesity

<table>
<thead>
<tr>
<th></th>
<th>Fraction of Sample</th>
<th>% Obese</th>
<th>% Overweight, never obese</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHANES 2007-8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>1.000</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>2-4 years</td>
<td>0.194</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>5-10 years</td>
<td>0.349</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>11-17 years</td>
<td>0.457</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td><strong>Multi-site EHR Data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>1.000</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>2-4 years</td>
<td>0.280&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>5-10 years</td>
<td>0.418&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>11-17 years</td>
<td>0.374&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20</td>
<td>17</td>
</tr>
</tbody>
</table>
But, Pediatricians...
MICROBIOME AFFECTS OBESITY

• Lower diversity of gut microbes associated with obesity
• Specific types of microbes associated with more or less obesity

• Microbiome may
  • influence energy metabolism
  • influence immune response, and other diseases directly
  • influence appetite and behavior
**Potential Critical Period**

- Established early in life
  - Parental effect – genetics or environment?
- Plasticity is not well understood

- Some tantalizing hints:
  - Change in diet associated with change in microbiome
  - Transplants of gut microbes tested – initial effects, but not persistent
  - Mice given antibiotics around birth of pups have more obese pups
How do Antibiotics Fit In?

• It’s possible that early childhood represents a particular “window” for establishing one’s microbiome
• Unclear whether things that change microbiome might have a short-term or long-term effect
• Unclear what one might do to change that

• We do know antibiotics given to treat infections also have a significant effect on gut microbes
• Might this effect change risk of obesity?
  • Prior studies of two European birth cohorts suggest a connection
UK Birth Cohort

• Followed 11,500 children from birth
  • 93% Caucasian, “slightly more affluent than the general UK population”
• Asked parents to recall antibiotic usage
• Gathered information on lifestyle, family, activity
• Growth measurements taken directly

• Found 22% increase in obesity risk at 3 yo if antibiotics taken in first six months after birth
• Found slightly higher BMI at 7 yo if antibiotics taken 15-23 months after birth

Trasande, Int J Obesity 2013
Danish Birth Cohort

- Followed 28,354 children from birth
- Asked parents to recall antibiotic usage
- Questionnaire at 7 years old

- Found 54% increase in overweight risk at 7 yo if antibiotics taken in first six months after birth AND mother was not overweight
- Found 46% decrease in overweight risk at 7 yo if antibiotics taken in first six months after birth AND mother was overweight

Ajslev, Int J Obesity 2011
Observational Study Design

- CHOP primary care patients in past 15 years
- Data on antibiotics in first two years after birth
  - Prescription records from EHR
  - Categorization – based both on spectrum and clinical guidelines
    - Narrow spectrum = pcn + amox
    - Broad spectrum = other systemic antibacterials
- Data on BMI in the next three years
  - Primary measurements
  - Conservative imputation of height
  - Outcome scored on max BMI Z-score using NHANES 2000 norms
**STUDY POPULATION**

- 65,000 children
- First visit 0-12 months old
- 33% urban
- 49% racial/ethnic minority
- 41% public insurance
- 61% with full 5 years follow-up
Antibiotics are common

Age (mo) at First Exposure
- 0 – 5 mo
- 6 – 11 mo
- 12 – 17 mo
- 18 – 23 mo
- None

Number of Children

Antibiotic Class
- All
- Narrow
- Broad
ANTIBIOTICS ARE COMMON

Number of Exposures
- 4+
- 3
- 2
- 1
- 0

Number of children

Antibiotic Class
- All
- Narrow
- Broad

0 10,000 20,000 30,000 40,000 50,000 60,000 70,000
<table>
<thead>
<tr>
<th>Associated</th>
<th>NOT Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>Race</td>
</tr>
<tr>
<td><em>Hispanic ethnicity</em></td>
<td>Urban/suburban practice</td>
</tr>
<tr>
<td>More doctor’s visits</td>
<td>Common infections</td>
</tr>
<tr>
<td><em>Public insurance</em></td>
<td>Bronchiolitis</td>
</tr>
<tr>
<td><em>Asthma</em>/wheezing</td>
<td>Anti-reflux medication usage</td>
</tr>
<tr>
<td>Steroid usage</td>
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</tbody>
</table>
ACCOUNTING FOR OTHER FACTORS

Variable

Hazard Ratio

0.9 1.0 1.1 1.2 1.3

Any 1 abx
Any 2 abx
Any 3 abx
Any 4 abx

Broad-spectrum 1 abx
Broad-spectrum 2 abx
Broad-spectrum 3 abx
Broad-spectrum 4 abx

Narrow-spectrum 1 abx
Narrow-spectrum 2 abx
Narrow-spectrum 3 abx
Narrow-spectrum 4 abx
Conclusions

• Antibiotics early in childhood are associated with small but persistent increase in obesity 1-4 years later
  • Most antibiotics prescribed for common indications
  • Majority of association appears to be with broader-spectrum antibiotics

• If there is a causal connection, will be interesting to see whether this occurs via the microbiome – other studies investigating this
Caveats

- Observational study design
- Unable to account for lifestyle factors
- Relatively small effect sizes
- Potential local effects
“Take-Aways”

- There isn’t likely to be a “silver bullet” to reduce obesity
- Addressing it as a health problem will require lots of small steps
- Careful antibiotic use may be one of these
  - Antibiotics are valuable, but they have unintended effects
  - Adherence to clinical guidelines may have additional benefits
- May fit into a bigger picture around establishing a healthy microbiome in early childhood